The State of New Hampshire
DEPARTMENT OF ENVIRONMENTAL SERVICES

Robert R. Scott, Commissioner

Rules Related to Per- and Polyfluoroalkyl Substances (PFAS):
FP 2019-14, Env-Wq 402 amendments
FP 2019-15, Env-Or 603.03 amendments
FP 2019-16, Env-Dw 700-800 amendments

Summary of Comments on Initial Proposals with NHDES Responses
June 28, 2019

Three sets of proposed rules and rule amendments relate to four per- and polyfluoroalkyl substances (PFAS), specifically perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), perfluorooctane sulfonic acid (PFOS), and perfluorooctanoic acid (PFOA). The three sets of rules are as follows:

Env-Dw 700 & 800 (FP 2019-16) establishes maximum contaminant levels (MCLs, the drinking water standards with which public water systems must comply) for the four PFAS in public drinking water and adds monitoring, compliance, reporting, and public notice requirements for the four PFAS;

Env-Or 603.03 (FP 2019-15) establishes ambient groundwater quality standards (AGQS), for the four PFAS, that are required by statute to be equivalent to the MCLs established in Env-Wq 700; and

Env-Wq 402 (FP 2019-14) establishes water quality standards and procedures for discharges to groundwater of wastewater containing any of the four PFAS.

The purpose of this document is to summarize the comments NHDES received from the public on all three proposed rules and to identify the changes made to the proposed rules in response to the comments or explain the reason(s) why NHDES did not make changes. Comments received that were unrelated to the proposed rules are not addressed in this document. To provide a foundation for the comments and responses, brief explanations of the purpose of the rules and of the rulemaking process are provided, as well as a summary of the main provisions of the rules and an explanation of how the currently proposed MCLs/AGQS were derived. A list of commenters on the rules and all written comments received concerning the rules as well as the transcripts for the three public hearings can be found on the NHDES website by searching on "PFAS".

OLS also provided written comments, which have been addressed.

Purpose of Proposed Rules

Env-Dw 700 & 800 establishes MCLs and monitoring, compliance, reporting and public notice requirements for the four health-related regulated PFAS ("health-regulated PFAS") that will apply to all non-transient public water systems, as required by RSA 485:16-e. The final proposed MCLs and AGQSs are:

Contaminant	Final Proposed MCL/AGQS (Part Per Trillion (ppt))
PFHxS	18 ppt
PFNA	11 ppt
PFOS	15 ppt
PFOA	12 ppt

The rules also eliminate the requirement for the owner or operator (O/O) of a laboratory that is seeking approval for an alternate analysis method to identify the specific PWS for which the alternate method would be used, meaning that once an alternate method is approved, it could be used for any PWS.

Env-Or 603.03 is being amended to change the existing AGQS for PFOA and PFOS and to add AGQS for PFNA and PFHxS. As required by RSA 485-C:6, those AGQS are identical to the MCLs that are proposed to be established under Env-Dw 700.

Env-Wq 402 is being amended to establish requirements for discharges to groundwater of wastewater containing any of the four PFAS. Those requirements reflect the proposed changes to the AGQS that would be established under Env-Or 603.03 and are intended to accommodate the lack of available technology to treat large quantities of wastewater that is contaminated with certain PFAS. Specifically, the rules would:

(1) Include residual PFOA, PFOS, PFNA, and PFHxS in the existing conditional exemption for meeting AGQS under certain circumstances;

(2) Establish a discharge limit for PFOA, PFOS, PFNA, and PFHxS in wastewater discharged to groundwater;

(3) Account for exceedances of the applicable limits for PFOA, PFOS, PFNA, and PFHxS; and

(4) Include PFOA, PFOS, PFNA, and PFHxS in the treatment/alternative response requirements established for 1,4-dioxane which includes identifying and eliminating contributing discharges to the wastewater stream.

Summary of Rule Development Process

Laws of 2018, Ch. 345 directed NHDES to initiate rulemaking related to PFOA, PFOS, PFHxS and PFNA by January 1, 2019, to:

(1) Establish MCLs for PFOA, PFOS, PFNA and PFHxS; and

(2) Re-evaluate the current AGQSs for PFOA and PFOS, which currently is 70 ppt combined, and to establish AGQSs for PFHxS and PFNA. AGQSs are clean-up standards for contaminated sites. Existing law (RSA 485-C:6) has always required an AGQS to be the same as any established MCL for a contaminant. The AGQS are also used to determine appropriate discharge limits for groundwater discharge permits.

The law provided funding for a toxicologist and health risk assessor position, which were filled in October of 2018. Also in October, NHDES held three technical sessions -- in Concord, Merrimack and Portsmouth (Pease Tradeport) -- to provide stakeholders with the opportunity to submit or identify studies and research pertinent to deriving health based standards and addressing other considerations required by law, including occurrence, ability to detect and treat as well as the anticipated costs and benefits. After careful review of appropriate studies and other states' approaches, NHDES began rulemaking by filing a Request for Fiscal Impact Statement with the Legislative Budget Assistant (*see* RSA 541-A:5) on December 31, 2018.

The initial proposal included the following levels for MCLs and AGQSs:

Contaminant	**Initial Proposed MCL/AGQS** (Part Per Trillion (ppt))
PFHxS	85 ppt
PFNA	23 ppt
PFOS	70 ppt
PFOA	38 ppt
PFOA & PFOS Combined	70 ppt

In conjunction with initiating the rulemaking, NHDES issued the "Summary Report on the New Hampshire Department of Environmental Services Development of Maximum Contaminant Levels and Ambient Groundwater Quality Standards for Perfluorooctane sulfonic Acid (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorononanoic Acid (PFNA), and Perfluorohexane sulfonic Acid (PFHxS)" on January 4, 2019 ("January 2019 Report").

After filing the initial proposed rules and rulemaking notices, NHDES held public meetings in Merrimack and Portsmouth (Pease Tradeport) to explain how the proposed standards were derived. The public hearings on the

proposed rules required by RSA 541-A were held in early March 2019 in Merrimack, Portsmouth and Concord. In addition to soliciting comments on the initial proposal, participants were asked to comment on the use of a toxicokinetic model developed by the Minnesota Department of Health ("MN model") to assess blood serum levels of people exposed to PFOA, including breastfed and bottle-fed infants. In the press release announcing the public hearings, NHDES informed interested parties that a preliminary assessment indicated that using the model would likely lower the proposed standards.

The final proposed rules reflect further research and new studies, the use of the MN model, consideration of comments received, discussions with other state and academic toxicologists, and professional judgement on what health-based standards will be sufficiently protective of human health over all life stages. While NHDES is unable to quantify all the costs and benefits associated with these proposed rules due to the emerging nature of these contaminants and the science related to them, after considering what currently is known about costs and benefits NHDES believes that the benefit of adopting these rules is not outweighed by the costs of implementing the proposed health based standards.

Summary of Significant Differences Between Initial and Final Rulemaking Proposals

1. The proposed MCLs/AGQSs have been lowered, primarily due to using the MN model.

2. The term "per- and polyfluoroalkyl substances (PFAS)" has replaced the term "perfluorinated compounds (PFCs)" throughout the document. PFAS is the more inclusive term and was used in most of the comments received, even though the rules currently do not include any polyfluorinated compounds.

3. The implementation requirements for public water systems have changed to reduce initial sampling frequency to two quarters if both samples come back with non-detects and to limit the maximum time between performing sampling to three years.

Technical Explanation of Proposed Lower MCLs/AGQSs and Updated Costs and Benefit Information:

Attachment 1 is "New Hampshire Department of Environmental Services Technical Background for the June 2019 Proposed Maximum Contaminant Levels (MCLs) and Ambient Groundwater Quality Standards (AGQSs) for Perfluorooctane sulfonic Acid (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorononanoic Acid (PFNA), and Perfluorohexane sulfonic Acid (PFHxS)" dated June 28, 2019 ("June 2019 Report"). It also includes findings of a peer review of NHDES's derivations conducted by Stephen M. Roberts, Ph.D.

Attachment 2 is an update on cost and benefit considerations.

Comments and Responses

General and technical comments concerning this rulemaking are categorized and listed below. Note that in addition to revisions discussed below, revisions have been made to each of the rules put the four compounds in alphabetical order.

General Comments Related to Proposed MCLs/AGQSs

Comments: The proposed MCLs and AGQS should be lower. A number of comments suggested the standards should be at 1 ppt combined. Others suggested that NHDES should adopt the lower advisory numbers adopted by other states or, in the case of New Jersey, its MCL for PFNA.

The proposed MCLs and AGQS should be higher. A few comments were received that urged NHDES to look at recently established health advisories in Canada and elsewhere that would increase the standards initially proposed.

Response: NHDES considered all of these comments and carefully reviewed all existing advisories and standards set elsewhere. However, the process used by NHDES incorporates long-established methodologies for setting standards that use the most current, defensible science and incorporates expert professional judgements. The resulting proposed standards are protective of human health at all life stages. Specific criticisms of factors used in the derivation of the standards are in the technical comments table.

Comment: NHDES did not have sufficient time, resources, or expertise to derive the standards and should collaborate with other state toxicologists and health risk assessment teams working on health advisories and standards.

Response: A full time toxicologist and a full-time and part-time health risk assessor along with contractor support and collaboration with academic, state, and federal agency health risk assessors and toxicologists provided the necessary expertise and effort to derive the standards for the final proposed rules. Their work and that of others at NHDES included routine meetings through state organizations such as Environmental Council of the States, Association of State Drinking Water Administrators, Northeast Waste Management Officials Organization, New England Interstate Water Pollution Control Commission, Interstate Technical and Regulatory Council, and the Federal-State Toxicology Risk Assessment Committee, all of which enhanced the agency's ability to meet the deadlines established by law. Because of the emerging nature of these contaminants, limitations are inherent in the amount of data and research available. NHDES made full use of available experts, science, and occurrence data in development of these proposed rules.

Comment: Laboratories cannot achieve a 2 part per trillion (ppt) reporting limit.

Response: NHDES has confirmed with the NH Environmental Laboratory Accreditation Program (NH ELAP) and the U.S. Environmental Protection Agency that a 2 ppt reporting limit is achievable.

Comment: NHDES should set a Maximum Contaminant Limit Goal (MCLG) for all PFAS at zero.

Response: NHDES agrees that there should be no man-made contaminants in New Hampshire's drinking water. However, these rules apply only to PFOA, PFOA, PFHxS, and PFNA, not the large class of chemicals to which they belong (*i.e.*, PFAS). The initial proposal included an MCLG of zero for each contaminant, which is consistent with the MCLG for other man-made chemicals and which is retained in the final proposed rules.

Comment: NHDES should review the science on PFAS every 2 years.

Response: Laws of 2018, Ch. 345 requires NHDES to review all AGQS every five years. Because of the evolving science related to PFAS, NHDES's health risk assessment team will monitor the science on an ongoing basis and will update the relevant rules as needed.

Comment: NHDES should have another public comment period if the standards change.

Response: NHDES solicited extensive public input and held three public hearings on the initial proposal, which resulted in 857 pages of comments on the rules. NHDES believes another public comment period will unduly delay adoption of the drinking water and ground water standards while providing few new perspectives that would alter the final proposed rules. Given the evolving nature of the science on these compounds, NHDES recognizes that revisions of the current rules to reflect new science may occur.

Comment: A Treatment Technique should be specified for these contaminants verses setting individual MCLs.

Response: A Treatment Technique is a tool under the state and federal Safe Drinking Water Acts used to lower the exposure to a contaminant through drinking water when an MCL cannot be set, which is not the case for these compounds. In addition, RSA 345 directs the NHDES to set an MCL for PFOA, PFOS, PFHxS, and PFNA.

General Comments Related to Costs and Benefits

Comment: The costs and benefits to affected parties that will result from establishing the new standards were not adequately quantified, did not follow federal requirements related to adopting MCLs, and did not identify the marginal costs and benefits at different MCL levels for each contaminant.

Response: Because NHDES was mandated by the Legislature to establish the MCLs and AGQS, any costs attributable to the standards are directly attributable to the law, not the rules. However, NHDES was able to estimate certain costs associated with standards for the four PFAS as explained in the January 2019 Report. These costs have been updated as shown in Attachment 2 for the final proposed MCLs and AGQS.

NHDES was not able to quantify the benefits (*e.g.*, avoided health care costs) in the initial proposal but was able to qualitatively explain the types of benefits that would result, and a future quantification may be possible (as explained in the January 4, 2019 report). In Attachment 2, NHDES has provided a summary of a recent report prepared by the Nordic Council of Ministers "The cost of Inaction: A socioeconomic analysis of environmental and health impacts linked to exposure to PFAS". This document provides further evidence of the benefits of setting health-based standards for these compounds that are protective of human health at all life stages, although NHDES could not directly estimate benefit for these four specific compounds for NH citizens using the report's methodologies. NHDES also provides information on a study that estimates costs related to low birthweight: "Perfluorooctanoic acid and low birth weight: Estimates of US attributable burden and economic costs from 2003 through 2014".

NHDES interprets the language in the statute regarding costs and benefits as a requirement to quantitatively estimate cost and benefit so far as the data is available to do so and to consider all that is known related to cost and benefit. Where needed data is lacking, NHDES has provided a qualitative description of what is known related to cost and benefit that was considered for this rule. The NH Department of Justice was consulted regarding the interpretation of some commenters regarding the lack of a comprehensive cost benefit analysis and identification of marginal costs consistent with federal procedures. The Office of the Attorney General found NHDES's interpretation of the requirement under RSA 485:3, I(b) to be reasonable and lawful (see Attachment 3). Because of the emerging nature and limitations of data for these chemicals and their impact to health, the quantification necessary to perform an analysis beyond what is currently provided for costs and benefits is not possible.

Comment: *Costs and benefits were not considered in establishing the proposed standards.*

Response: NHDES considered what is known about costs and benefits and determined that using the health-based numbers is appropriate, achievable, and necessary to protect human health at all life stages, as required by Laws of 2018, Ch. 345.

Comment: *Benefits can be calculated by assuming PFAS causes cancer.*

Response: The links between PFOA, PFOS, PFHxS, or PFNA and cancer are not sufficiently clear; it is not appropriate to base benefit on a health outcome that is still being studied.

Comment: *Costs are largely born by municipalities for landfill, fire station, wastewater residuals, and public drinking water system compliance with the new standards. The state should pay for these costs.*

Response: NHDES recognizes that there will be significant costs to municipalities resulting from the legislative directive to establish standards. Cost considerations are reflected in the proposed reduction in sampling required at public water systems to demonstrate that ongoing reduced sampling is appropriate. Also, the proposed provisions that will allow groundwater discharges containing PFAS above twice AGQS to occur in certain circumstances (*i.e.*, only if no impacted wells) provided that likely sources of PFAS are identified and eliminated, reflects the reality that municipalities need to economically discharge wastewater. There is currently no new source of state funding established to assist municipalities with the costs associated with the rules. Capital costs for public water system compliance with the new MCLs will be eligible for existing state and federal low interest loan and grant funds.

Comment: *Costs to small and rural public water systems with fewer customers will be significant.*

Response: NHDES agrees that Laws of 2018, Ch. 345 resulted in costs related to achieving compliance with the MCL for all public water systems, and that small systems have a smaller rate base to absorb cost increases. This has always been true for small systems, which under the federal and state Safe Drinking Water Acts must comply with all MCLs. Low interest loans and grants from the Drinking Water State Revolving Fund and other state and federal sources will continue to be available to small systems.

Comment: *NHDES should alter cost estimates for public water systems based on a study prepared for Merrimack Village District (MVD) and should make assumptions based on the potential use of more expensive technologies, variations in water quality, and the potential increases in costs to systems already*

treating rather than using the range of actual treatment and ongoing cost approach described in the January 4, 2019 report.

Response: NHDES reviewed the study prepared by Underwood Engineering for MVD and found the estimates consistent with those used to estimate costs in the January 2019 Report, as supplemented by the update in Attachment 2. NHDES considered all comments related to the assumption that the range of initial treatment and annual costs can be based on what actual costs have been incurred by public water systems. After doing so, NHDES continues to believe that this approach is the best way to quantify both initial treatment and ongoing costs. This approach includes both new technologies and granular activated carbon; NHDES believes those instances where more expensive treatment is selected is balanced by systems that will choose to blend, interconnect with another system, or take contaminated wells off line. Similarly, the annual cost estimate includes systems achieving water quality at lower levels than is required by the current AGQS and is potentially an overestimation for systems which may choose to blend, interconnect, or take a well off line rather than treat.

Comment: NHDES should have provided an order of magnitude or contingency cost for the potential sources of contamination for which they could not quantify costs due to insufficient data.

Response: Because of limited testing to date at a number of potential sources (*e.g.*, fire stations, oil remediation sites, biosolids/sludge/septage processing and application sites, air deposition sites, *etc*.), NHDES was unable to estimate the costs that could be associated with them. This same lack of information precluded the derivation of a possible contingency figure. Since that time NHDES has continued to investigate PFAS occurrence and has an improved data set for certain sources. For instance, while the initial report indicated that as many as one third of fire stations may have caused PFAS contamination in nearby wells through the use and storage of fire-fighting foams, more recent data indicates a much lower occurrence. Also, additional testing at oil remediation sites indicates little association of PFAS occurrence.

Comment: NHDES should have quantified costs that may occur due to establishing AGQSs and MCLs associated with residential septic tanks, residual management, leachate disposal, and landfill gas.

Response: NHDES does not have sufficient data to determine if these potential sources would result in a violation of the MCLs/AGQS being proposed, nor is there sufficient occurrence data to estimate costs.

Comment: NHDES should provide the present value of long-term monitoring on sites with a groundwater management permit that violate an AGQS for any of these compounds.

Response: Because of the persistent nature of these chemicals, costs associated with monitoring to ensure permit compliance is likely to be longer term than for more biodegradable contaminants. There is insufficient data to determine the length of time to be used in such a calculation, but NHDES acknowledges that the annual cost estimated will continue for many years.

Comment: The three rules create an unfunded mandate that is a violation of Article 28-a of New Hampshire's Constitution and RSA 541-A.

Response: The costs of implementing the rules are not attributable to the rules, but derive directly from the statutory mandate for NHDES to adopt standards. Because the costs are exclusively attributable to Laws of 2018, Ch. 345, the rules do not violate Part I, Article 28-a of the New Hampshire Constitution.

However, even if costs could be attributable to the rules, the costs are within the scope of modifications allowable under *City of Concord v. State of New Hampshire*, 164 N.H. 130 (N.H. 2012). In *City of Concord*, the Court reviewed all prior decisions on the same issue and concluded that:

> Collectively, these cases stand for the proposition that where a local subdivision has historically had responsibility for the subject matter of the mandate, some change in the scope of that responsibility does not result in a violation of Article 28-a.

City of Concord at 140 (footnote omitted). The Court further stated "Accordingly, we conclude that to constitute a new, expanded or modified 'responsibility,' the state action must impose some **substantive**

change to an underlying function, duty or activity performed or to be performed by local government." *Id.* at 141-142 (emphasis added).

Because municipalities and other political subdivisions historically have been required to test the drinking water supplied to the public for contaminants, the addition of the PFAS contaminants to the list of required testing does not violate Part I, Article 28-a.

For the same reasons, the rules do not violate RSA 541-A:25. RSA 541-A:25, I simply restates Part I, Article 28-a and then adds that programs covered include "those municipal functions which might be undertaken by a municipality or by a private entity and those functions which a municipality may legally choose not to undertake." RSA 541-A:25, III. The analysis in *City of Concord* does not depend on whether a political subdivision is legally required to undertake a program or responsibility, and so applies to RSA 541-A:25 as well.

Comments Related to Occurrence and Contamination

Comment: There is not sufficient occurrence data to determine the need for MCLs/AGQSs.

Response: NHDES and others have done extensive sampling throughout New Hampshire that includes public water systems, wells near many likely sources of PFAS contamination, and wells in areas that do not have likely sources of contamination. The occurrence data is described in the January 2019 Report. Since January, additional contamination at public water systems, hazardous waste sites, landfills, and other potential sources has been documented.

Comment: Contamination should be treated differently if from a diffuse source versus contamination related to industrial activity and the use of fire-fighting foams.

Response: NHDES statutes related to waste sites do not distinguish between sources of contamination.

Comment Related to Studies Received

Comment/Response: NHDES was provided with numerous studies for consideration in the derivation of the standards and a few references for establishing benefits. To the extent the health studies were relevant to PFOA, PFOS, PFNA, and PFHxS, they were reviewed by the health risk assessment team. The bibliography of health studies used in derivation of the standard can be found in the June 2019 Report.

Comments Related to MCL Implementation at Public Water Systems (Env-Dw 700 & 800)

Comment: The rules should align with initial monitoring precedents set in the NH Code of Administrative Rules for radionuclides and synthetic organic compounds (SOC), which allow the ongoing routine monitoring schedule to be determined after two quarters of non-detects versus four quarters.

Response: NHDES agrees with this comment and has revised the rule accordingly.

Comment: The proposed monitoring frequency is not protective of public health. Quarterly sampling should be required for any detection and annual sampling should occur at all public water systems.

Response: NHDES agrees that due to the ubiquitous nature of these four PFAS and the proposed lower MCL standards, the sampling frequency in the proposed initial rules may be insufficient. The rules have been changed to require quarterly sampling for systems with sample results above an MCL or systems with treatment to remove PFAS, annual sampling for systems with sample results greater than 50% of the MCL up to the MCL, and monitoring every three years for systems with sample results less than or equal to 50% of the MCL.

Comment: Env-Dw 712.23 (c) and (d) should be eliminated because they are too vague and unnecessarily complicate a determination of compliance.

Response: This is identical to language required for VOCs. However, the language has been eliminated as statistical variations of concern can be addressed under Env-Dw 708.01(d).

Comment: Tables 712-1 and 712-2 should contain consistent terminology.

Response: The two tables do not overlap, so it is unclear what terminology is not consistent.

Comment: Public Water Systems will need assistance with implementation and communication related to the new MCLs.

Response: NHDES intends to continue to work with public water systems and their trade organizations to understand what is required by the rules and to effectively communicate that with their customers about PFAS and the new rules.

Comments applicable to Groundwater Discharge Permit Rules (Env-Wq 402)

Comment: There should be no exception in the rules for discharges of wastewater containing PFAS to groundwater that result in exceedances beyond the groundwater management zone as is now allowed for 1,4 dioxane. Specifically, if no wells are impacted, the rule would allow the permittee to identify and eliminate the PFAS versus halting the discharge.

Response: Because of both the current inability of treating large quantities of wastewater and the need for wastewater disposal, NHDES believes that this provision is necessary and is in keeping with the pre-treatment requirements in the Clean Water Act.

Comment: Requiring the AGQS to be met in treated wastewater being discharged to groundwater eliminates the opportunity for the level to naturally decline prior to reaching the boundary.

Response: The intent of establishing the values in Table 402-2 for treated wastewater effluent being discharged to groundwater is to assess the likelihood of whether one or more facilities that are connected to a wastewater treatment facility are contributing substantially high concentrations PFAS discharges to its incoming wastewater stream that, in turn, result in high PFAS concentration in its effluent discharged to groundwater, which then results in a groundwater quality standard violation. Based on a limited dataset of PFAS results in influent and effluent at wastewater treatment facilities, establishing the threshold values in Table 402-2 at twice the revised proposed MCLs "weeds out" wastewater treatment facilities that have low concentrations of PFAS in their incoming wastewater stream that are likely related to domestic-consumer wastewater discharges only. Wastewater treatment facilities that are known to NHDES as having have individual connections to their sewer systems that contribute high PFAS loads have substantially higher PFAS concentrations in its treated wastewater effluent and will by captured by the revised values in table 402-2 (*i.e.*, twice the proposed standards).

Comment: NHDES' proposed rules related to the discharge to groundwater of wastewater containing PFAS fail to properly protect public health.

Response: The proposed rules specifically require that sources of drinking water be fully protected from potential contamination associated with groundwater discharges. The proposed groundwater discharge rules protect New Hampshire's groundwater by:

- Ensuring that permittees:
  (1) Monitor groundwater quality around permitted discharge sites;
  (2) Not cause any private or public drinking water supply sources to be contaminated by PFOA, PFOS, PFNA, or PFHxS at concentrations that exceed the proposed MCLs; and
  (3) Provide treatment or alternative drinking water when sources of water that have been contaminated at levels above the MCL due to the permittee's discharge.
- Requiring that permittees reduce the concentration of PFOA, PFOS, PFNA, and PFHxS in wastewater that is discharged to groundwater by reducing or eliminating discharges of these compounds into the wastewater system.
- Limiting the maximum amount of PFOA, PFOS, PFHxS, and PFNA that is allowed to be discharged to groundwater.

- Ensuring no groundwater discharge contributes to a violation of surface water quality standards. That is, should New Hampshire adopt a surface water quality standard for PFAS in the future, permitted groundwater discharges impacting surface water will be subject to these standards.

These actions, along with the reduction and/or phase-out of the use of these compounds in commerce, will help to ensure groundwater quality will be improved and protected at permitted discharge sites. NHDES does not agree that the proposed rules should require treatment based on the potential for the development of future technologies capable of treating large quantities of wastewater at a public wastewater treatment plant are not currently available.

General Comments Related to Health-Based Risk Assessment[1]

Comment: NHDES should have derived a health-protective drinking water value based on cancer effects in animal studies instead of non-cancer health effects.

Response: NHDES reviewed both human and animal studies investigating the cancer-causing potential for PFOA and PFOS. There are currently no peer-reviewed and published rodent model cancer studies for PFNA or PFHxS. There is limited evidence associating PFOA and PFOS with altered cancer risk, and the uncertainties of this were discussed in the January 2019 Report as well as other agencies (EPA 2006; EPA 2016ab; MDH 2017; ATSDR 2018). The U.S. EPA (EPA) has classified the carcinogenic potential of PFOA and PFOS as "suggestive", which is the lowest cancer classification category given the evidence for human cancer potential (EPA 2016ab).

EPA and the New Jersey Drinking Water Quality Institute (NJDWQI) have developed different numerical cancer guidelines for PFOA based on testicular cancer set at a one-in-one million cancer risk for a 70-year exposure from drinking water. In 2016, EPA determined a cancer value of 500 ng/L (EPA 2016a), while the following year NJDWQI calculated a different cancer value of 14 ng/L (NJDWQI 2017). The difference in calculated values is due to the limited quality of the available studies and variations in toxicokinetic adjustments. Regardless of which value is more accurate, the proposed PFOA MCL of 12 ng/L based on a non-cancer endpoint is below the more conservative of the aforementioned values (14 ng/L; NJDWQI 2017). The PFOS cancer evidence is even more uncertain than that of PFOA and not adequate for quantitative evaluation. Should federal agencies make new determinations about the carcinogenicity of these compounds, or should new studies arise that present clear evidence of carcinogenic potential in humans, NHDES will evaluate the new information and take such action as is appropriate.

Cancer is a complex and multifactorial group of diseases. Regional differences in cancer rates may be due to the interaction of multiple factors, including individual lifestyle choices, genetic susceptibility factors, and variations in exposure to physical, chemical, and biological agents in the environment. Based on the currently-available evidence, NHDES determined that a non-cancer health endpoint was more sensitive and more reliable for developing a health protective standard. NHDES agrees that additional research is needed to understand the broader health impacts of these contaminants on outcomes, including cancer.

Comment: The proposed MCLs should be protective across all human life stages, including but not limited to fetuses, neonates, infants and children.

Response: NHDES's adoption of the transgenerational model for the currently proposed MCLs is intended to be protective of all life stages. The exposure estimates used are from the 95th percentile water consumers, which is additionally protective for typical (average) water consumers. The use of the transgenerational model allows for determination of an MCL with a margin of safety across all life stages based on consideration of the health studies and toxicological reviews (*e.g.*, ATSDR 2018) evaluated by NHDES. The predicted contributions of drinking water to blood concentrations at the proposed MCLs are similar to background levels reported by the National Health and Nutrition Examination Survey (NHANES).

Additionally, NHDES selected critical health effects from animal studies based on sound evidence for human health relevance and were equally or more sensitive than developmental or teratogenic effects

[1] List of references begins on page 21.

observed in rodents. The human health relevance of many toxic responses observed in rodents is an ongoing area of research, and subject of debate amongst toxicologists because of a currently limited understanding of which species is more sensitive to PFAS at identical internal doses. Some developmental effects in rodents have been reported at remarkably lower doses of certain PFAS (*e.g.*, delayed mammary gland development in response to PFOA), and similar to NHDES, other agencies have declined to use these endpoints as the basis of their risk assessments and subsequent drinking water values (MDH 2017; NJDWQI 2017; EPA 2016a; ATSDR 2018; MIDHHS 2019). As concluded by other agencies, the cross-sectional or ecological studies of human health effects do not provide a sound basis for reference dose (RfD) determination, or demonstration of causality, and were therefore not used for direct calculation of RfDs. Such studies were used for evaluating the potential human health relevance of reported effects in animal studies.

Comment: *NHDES should be regulating all PFAS that are now in some people's drinking water.*

Response: In 2018, the Legislature decided that sufficient scientific information existed to determine whether the four PFAS covered by this rulemaking posed a health risk in drinking water, and mandated this rulemaking in Laws of 2018. Ch. 345. The Agency for Toxic Substances and Disease Registry (ATSDR) did not derive MRLs for other PFAS such as GenX, PFHpA, PFHxA, *etc*. NHDES is reviewing emerging studies to determine whether there is sufficient data to derive reference doses for other PFAS; this work includes consideration of draft toxicity assessments from EPA for PFBS and GenX. The work also includes consideration of future RfDs proposed by the EPA through the Integrated Risk Information System (IRIS) program for the following PFAS: PFBA, PFHxA, PFHxS, PFNA and PFDA.

Comment: *PFAS should be regulated as a "class" or "sub-class" and there should be a standard for total PFAS, or at least a combined standard for the four currently being regulated.*

Response: NHDES agrees that there is a need for an evidence-based class or subclass regulation of PFAS given the wide-spread occurrence and chemical diversity of this contaminant family. However, NHDES determined that differences in the most sensitive health effects, individual toxicokinetics and a lack of relative potency factors for PFAS do not support the assumption of identical (*i.e.*, 1-to-1) risks from exposure. Variation in the combinations of functional groups and carbon chain length appear to produce differences in biological activity (*e.g.* receptor and protein affinity) and the half-lives of individual PFAS. As discussed in the initial proposal (NHDES 2019), toxicity equivalency factors or other approaches have not been developed for this class of contaminants and highlights a critical research need. NHDES is aware that this is an active area of research and is therefore continuing to monitor publications on methods for this approach. Should a robust and scientifically-defensible approach to group regulation be developed, NHDES will consider its application in future development of drinking water standards for PFAS.

Comment: *The standards proposed by NHDES are different from the health advisory values, screening levels or MCLs developed by other states.*

Response: NHDES derived Maximum Contaminant Levels (MCLs) using standard EPA methodologies. Under the New Hampshire and federal Safe Drinking Water Acts, an MCL is the highest level of a contaminant that is allowed in drinking water delivered by public water systems. MCLs are enforceable standards (EPA 2018). To date, only New Jersey has established an MCL for any PFAS; for PFNA, at 13 ng/L (NJ DEP SRP 2019). Values developed by ATSDR (*e.g.*, Minimal Risk Levels (MRLs)) and other values derived in certain States (*e.g.*, Health Based Guidance Values (HBGVs)) are not enforceable and are largely intended to be used as guidance for site remediation and other public health responses.

NHDES understands the public's concerns regarding the initially proposed standards and the existing patchwork approach to regulatory standards for PFAS. This patchwork of regulatory standards underscores the need for action by EPA to harmonize standards for these wide-spread environmental contaminants.

The proposed final MCLs/AGQSs are similar to the standards set by other States, and are protective for the individual PFAS given the conservative exposure assumptions selected by NHDES. NHDES has collaborated and consulted with other states' health risk assessment teams that have been involved in deriving health advisories or are working towards setting MCLs. The collaborations included both formal

multistate conference calls and direct communications to discuss advances in PFAS toxicology and the rationale for each state's particular standard setting approach.

Comment: NHDES should apply the precautionary principle in their health-based risk assessment.

Response: The precautionary principle (PP) refers to a risk management strategy used by European Union countries when there is incomplete scientific knowledge of the risk to human health or the environment from chemicals/technologies. In the strictest interpretation, the PP recommends not using the substance or employing the technology at all until the risk is better understood. Like other U.S. state agencies, NHDES does not apply the PP as a default approach to health risk assessment of chemical contaminants.

NHDES did not apply the PP because application of the PP is inconsistent with risk assessments developed by other states and federal agencies (*e.g.*, US EPA and ATSDR). To date, no federal or state agencies have used the PP approach to develop PFAS drinking water criteria. Standard approaches used by federal and state agencies include weight-of-evidence considerations and the application of standard inputs for exposure considerations and uncertainty factors. The ubiquity of PFAS across environmental media makes application of the PP unreasonable. Furthermore, PFAS are already detected in the environment and a growing number of commercial and consumer products. NHDES's mandate is to use the best available scientific studies and data to determine concentrations in drinking water that will not present an appreciable health risk to water users throughout their lives. NHDES does not have the authority to ban PFAS from being used.

While NHDES did not conduct its assessment under the guidance of the precautionary principle, NHDES was conservative in its risk assessments of PFOA, PFOS, PFNA, and PFHxS. NHDES agrees that the proposed MCLs for PFAS should be based on exposure and effects in the most sensitive subpopulation to be protective of the broader population; that is the reason NHDES used the MN transgenerational toxicokinetic model to revise the initially proposed MCLs. In using the MN model, NHDES considered a protective reasonable exposure scenario of 12 months of exclusive breastfeeding. The 95th percentile ingestion rates were used for breastmilk consumption and water consumption across a lifetime. The newborn is the most exposed population due to placental transfer and subsequent exposure from breastfeeding or water-reconstituted formula at ingestion rates that are significantly higher for infants than for adults. Examples of upper level ingestion rate differences include: 1 to 3 months of age, water ingestion = 267 mL/kg-d; 1 to 3 months of age, breastmilk ingestion = 190 mL/kg-d; adult (21+ years), water ingestion = 44 mL/kg-d. Infants are also considered to be the most sensitive population to potential adverse health effects because of their rapidly developing bodies. Use of the MN transgenerational model to protect the most vulnerable population has significantly reduced the proposed MCLs and established a protective margin of exposure across a lifetime.

Comment: NHDES's proposed reference doses and MCLs are different from the CDC Agency for Toxic Substances and Disease Registry's (ATSDR) minimal risk levels and drinking water screening values.

Response: NHDES did not adopt the Agency for Toxic Substances and Disease Registry's (ATSDR) provisional minimal risk levels (MRLs) as the basis for its proposed maximum contaminant levels (MCLs) because: (1) MRLs are not synonymous with MCLs, (2) MRLs are developed by the CDC for use in screening impacted sites, and (3) NHDES determined different reference doses (RfDs) based on consideration of other sensitive health effects reported in animal studies. Additionally, the MRLs are currently only provisional, and are subject to change in response to public comments submitted on ATSDR's 2018 draft toxicological profile.

To the first point, an MRL is not developed to serve as an MCL or other actionable standard. As stated by the ATSDR:

> "These substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. **It is important to note that MRLs are not intended to define clean up or action levels for ATSDR or other Agencies**."- (ATSDR, 2018, emphasis in original)

An ATSDR MRL is used for screening environmental media and to make decisions about additional surveillance and study planning at a site. Exposure at or above an MRL screening value does not mean that adverse health effects will occur (ATSDR, 2018). Thus, acknowledging the intention behind MRL development and application, NHDES did not use the provisional ATSDR MRLs for MCL development.

Using EPA methodology, RfDs are developed for calculating actionable drinking water standards. There are several chemical substances whose MRL value is not identical to the corresponding RfD as proposed in the Integrated Risk Information System (IRIS) Database. In some cases, such as PFAS, the ATSDR MRL is lower than the RfDs proposed by the USEPA IRIS Database (*e.g.*, PFOA, PFOS, and benzene). In other cases, the MRL is a higher value than the more protective RfD values proposed using EPA methodology (*e.g.*, 1,4-dioxane and nitrate). Such differences can arise from the determination of human health relevance, application of uncertainty factors, and other technical considerations used to translate findings from animal studies into estimates for protecting human health. Based on its evaluation of peer-reviewed studies as well as risk assessment work conducted by other state and federal agencies, NHDES derived RfDs for PFOA, PFOS, PFNA and PFHxS with its justifications detailed in Section III of the June 2019 Report.

Comment: *NHDES should consider the roles of biological plausibility and reverse causation in the reported associations between PFAS and human health outcomes.*

Response: In its initial proposal and re-evaluation of human health evidence (*i.e.*, epidemiological studies), NHDES considered the issues of confounding factors and reverse causation as they related to associations between PFAS and human health outcomes. NHDES disagrees with the statement of one commenter, who asserts "*confounding and/or reverse causation which (have) been shown the likely explanation for several reported epidemiological associations*". NHDES acknowledges there are confounding factors and limitations to some of the existing epidemiological studies on PFAS-associated health impacts. These limitations in the currently available epidemiological database make it difficult to demonstrate causality between PFAS and certain health outcomes (reviewed by ATSDR, 2018). However, this does not dismiss the fact that PFAS possess biologically-active properties in humans and therefore necessitates determination of acceptable levels of exposure from drinking water.

Confounding factors are variables other than the variable of interest (*e.g.*, a PFAS) that can influence the health outcome under investigation. One example from epidemiological studies of PFAS is co-exposure to other environmental contaminants and stressors. Many epidemiological studies are cross-sectional in design, which means they cannot account for historic exposures to other chemical or physical agents. Other environmental contaminants that possess dramatically shorter half-lives than these four PFAS are unlikely to be measured and are therefore unaccounted for in statistical analyses. Arguably, this could result in associations between health outcomes and PFAS due to their long physiological half-lives when other chemicals, that have been eliminated from the body, may have contributed to or caused the health outcome. Similarly, another confounding factor is the interplay of multiple PFAS aside from PFOA, PFOS, PFNA, and PFHxS. There is clear evidence that other PFAS are present in the blood of the U.S. population (reviewed by ATSDR, 2018), but the lack of any toxicity data for the majority of these compounds presents a major source of uncertainty for risk assessors and serious concern for the broader public.

Regarding PFAS, reverse causation would occur when certain health conditions elevate internal concentrations of PFAS. This could result from a certain health condition impairing the body's ability to eliminate PFAS, resulting in a correlation between markers of the disease and PFAS despite PFAS having no role in the origins of the disease. An example of this was discussed by Dhingra *et al.* (2017) and the Michigan Panel (2018), where negative associations of PFAS (*i.e.*, PFOS and PFOA) with uric acid levels and estimated glomerular filtration rates may be the result of reverse causation as impaired kidney function would result in elevated serum PFAS concentrations. NHDES selected health effects for the proposed MCLs after consideration of evidence from human epidemiological studies, as well as supporting evidence from controlled animal studies that are not as prone to the issue of reverse causality.

Evidence from studies of populations across different geographies (*e.g.*, C8 in Ohio, Frisbee *et al.*, 2009, Winquist *et al.*, 2013; and the Danish National Birth Cohort, Olsen *et al.*, 2001; Ernst *et al.*, 2019) support

the contention that PFAS are associated with health markers at exposure levels seen in background, community drinking water, and occupational settings. As with many epidemiological studies, these have limitations and further research is required to clarify the relationship between PFAS and human health outcomes. NHDES used the existing evidence to protect public health given the widespread occurrence of PFAS, the significance of exposure from drinking water, and the lack of toxicity data for these and other PFAS. There is sufficient consistency between epidemiological studies and animal models to indicate that PFAS elicit adverse biological activity from certain organ systems (*e.g.*, liver, immune, endocrine, reproductive). As the existing scientific literature regarding the health effects of PFAS has not kept pace with their widespread applications and dispersal into the environment, NHDES expects future studies will improve our understanding of health effects and acceptable levels of exposure. NHDES will continue to review emerging science for the re-assessment of the MCLs within 5 years of implementing the finalized values and will take such action as is appropriate.

Comment: *Certain references should be updated, or were omitted, from the initial proposal.*

Response: NHDES has updated their list of health impacts to include those referenced on pages 5-6 of the 2018 draft ATSDR Toxicological Profile for Perfluoroalkyls. This updated list is found in the Executive Summary of the June 2019 Report.

The reference for "PPARa activation in humans does not result in the same peroxisome proliferation effects but does induce changes in lipid metabolism and gene transcription." is: Tyagi S, *et al.* 2011. The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. J. Adv. Pharm. Tech. Res., 2(4), 236-240.

The references for the human half-lives cited for PFOA (2.3-3.8 years) are (Olsen *et al.*, 2007; Bartell *et al.*, 2010); PFOS (5.4 years)(Olsen *et al.*, 2007; Bartell *et al.*, 2010); PFHxS (8.5 years)(Olsen *et al.*, 2007); PFNA (2.5 years)(Zhang *et al.*, 2013, ATSDR 2018). The reference for half-life data used in the calculations for PFOA, PFOS and PFHxS in the initial proposal is Li *et al.* 2018.

Comment: *In addition to these four PFAS NHDES needs to ban fluoride.*

Response: This rulemaking is not related to fluoride; it relates to regulatory standards for PFOA, PFOS, PFNA, and PFHxS. The four PFAS are organic compounds that contain fluorine. These organic compounds and their properties are distinctly different from fluoride (F^-), which is an anion or negatively charged element that is not synonymous with PFAS. Individual communities in NH determine their own drinking water fluoridation practices, and NHDES does not have authority over supplementation of fluoride into commercial personal care products.

Technical Comments Related to Application of the Minnesota Transgenerational Exposure Model (Goeden *et al.*, 2019)

Comment: *On February 21, 2019, NHDES solicited technical stakeholder input on the appropriateness of a toxicokinetic exposure model, or the Minnesota model (Goeden et al., 2019), for deriving the proposed MCLs. The majority of comments recommended its use based on technical merit, and a few commenters noting concerns with the model's limitations.*

Response: NHDES agreed with technical comments recommending the application of the transgenerational breastfeeding model developed by the Minnesota Department of Health (MN model). Details on the application of this model and factors applied by NHDES are found in the June 2019 Report.

After reviewing the MN model, NHDES concluded that this approach would be appropriately protective across all life stages after consideration of reasonable exposure scenarios. As discussed in the June 2019 Report, there are uncertainties and limitations with using this or any risk assessment tool for developing health-protective drinking water values. In spite of these uncertainties, NHDES has concluded that the extraordinary half-lives of these PFAS, combined with their transfer rates into breastmilk, merit consideration in the risk assessment supporting the proposed MCLs.

Some commenters urged the use of the unpublished version of this tool prior to its publication in January 2019 as the Minnesota Department of Health (MDH) had previously recommended non-MCL values for PFAS in drinking water. Scientific publications undergo a peer review process to ensure necessary feedback is garnered on methods, results, and conclusions, and the reviewers are tasked with assessing the quality of information in terms of both accuracy and validity. The document was undergoing the peer review and publication process at the time the initial MCLs were being developed for this rulemaking and did not follow traditional risk assessment methods. NHDES did not know what experts in modeling would have recommended or suggested based on their peer review of the model.

Until the current proposal by NHDES, this model has not been applied to determine protective health values for MCLs. NHDES acknowledges that this model, like other models, has existing data gaps (*i.e.*, it is a single compartment model). In a different model (Loccisano, *et al.*, 2013), several additional parameters were found to influence model predictions, including the liver:plasma partition coefficient, liver volume, maternal glomerular filtration rate, and the free fraction of PFOA in plasma. These limitations are discussed in further detail in the June 2019 Report. Incorporation of future studies on maternal transfer is expected to prove useful in refining this risk assessment tool, and NHDES will consider them when developing standards for PFAS in the future.

Other commenters have argued that this tool is not new nor "peer-reviewed" despite an informal review process (MDH 2017) conducted by MDH and subsequent peer-reviewed publication of the model (Goeden *et al.*, 2019). NHDES disagrees that this process does not constitute an adequate peer review of the model. After consideration of comments prepared by an external expert in physiological modeling, as well as consultation with MDH and other state risk assessment groups, NHDES concluded that this tool is appropriately vetted for use in developing health-protective drinking water standards.

Several critiques against the transgenerational model were essentially about the relative conservatism of the final drinking water value when considering the conservatism of the model variables and assumptions made in the RfD derivation. Similar to MDH, NHDES applied upper value estimates for the water ingestion rates of the mother and offspring, breastmilk ingestion rates, and duration of breastfeeding, all of which recommended a lower and more protective drinking water value. However, NHDES used central tendency values for the volume of distribution and half-life estimates, and limited the relative source contribution after consideration of the level of conservatism being applied to the exposure scenario. NHDES believes these considerations for the transgenerational model, and others detailed in the June 2019 Report, provide a sufficient level of protection without being hyper-conservative in its risk assessment.

<u>Comment</u>: *NHDES should reconsider whether its assumption that the water intake rate of lactating women is appropriately protective across a lifetime.*

<u>Response</u>: Several comments were submitted regarding the use of the 95th percentile water intake rate for lactating women as a part of the calculation of the MCL. The proposed MCLs no longer use the single fixed water ingestion rate of 0.055 L/kg-day, which is the estimated 95th percentile for a lactating woman (EPA, 2011). Given the use of the MN model, NHDES believes several of these comments have been addressed as the model incorporates different water ingestion rates (*e.g.*, infant, adolescent, and adult) over a lifetime instead of a single point estimate. To be consistent with its prior conservatism and fully protective of the entire population, NHDES applied upper value (95th percentile) breastmilk and drinking water ingestion rates within the transgenerational model.

As NHDES relied on the 2011 Exposure Factors Handbook in its prior recommendation, the new values for the drinking water ingestion rates from the 2019 Chapter 3 Update (EPA, 2019) were applied in place of the 2011 values (updated February 6, 2019). No update has been published for estimated breastmilk ingestion rates, so these were left unchanged in the transgenerational model. Table 3 of Section IV in the June 2019 Report lists these values as they were used in the model.

Because of the unique properties of PFAS and identified health impacts, NHDES applied the transgenerational model instead of the use of the standard 2 L/d assumption historically made by some state agencies. The highly bio-accumulative nature of PFAS requires consideration of age-specific drinking

water values as modeling clearly predicts prolonged elevations in blood concentrations of PFAS following early life exposure. The critical health effects from PFOA (liver damage), PFOS (immune suppression), PFNA (liver damage), and PFHxS (impaired female fertility) are considered to be chronic health effects in humans as a result of prolonged exposure. As NHDES is no longer using a developmental outcome (*e.g.*, for PFOS in the initial proposal), consideration of long-term serum levels as predicted by the MN model was deemed appropriate instead of relying on a single specific life stage.

Comment: *NHDES should select different serum half-life estimates for use in the Minnesota model and derivation of reference doses.*

Response: As a part of its re-evaluation of the proposed MCLs and consideration of scientifically-supported technical comments, NHDES revisited the physiological half-life estimates used for PFOA (now 2.3 years, Bartell *et al.*, 2010), PFOS (remained 3.4 years, Li *et al.*, 2018), PFNA (now 4.3 years, Zhang *et al.*, 2013) and PFHxS (now 4.7 years, Li *et al.*, 2018). The rationale behind these selections and their impact on the RfDs is detailed in Section III of the June 2019 Report.

The dosimetric adjustment factors that estimate external reference doses (RfDs) from internal serum levels use these half-lives to make chemical-specific estimates. The use of longer half-life values results in lower RfD values (see Section III of the June 2019 Report for mathematical operation, and Goeden *et al.*, 2019 for implications in the transgenerational model). This step accounts for the highly bio-accumulative nature of PFAS and has been used by other states (NJDWQI 2017, 2018; MDH 2017, 2019ab) and federal agencies (EPA 2016ab; ATSDR 2018) for estimating external doses of PFAS.

Certain commenters have asserted that this dosimetric adjustment factor approach is overly conservative, overestimating toxicity of PFAS by conflating bioaccumulation with toxicity in humans. NHDES disagrees. This step is necessary to account for the fact that low-level external exposures to these PFAS eventually result in chronic and elevated internal levels. Thus, this step is necessary to account for the unique and extraordinary half-lives of these PFAS reported in humans (Olsen *et al.*, 2007; Bartell *et al.*, 2010; Zhang *et al.*, 2013; Li *et al.*, 2018). If new methods are developed that can be applied to PFOA, PFOS, PFNA, and PFHxS, NHDES will consider these methods and take such action as is appropriate.

Comment: *NHDES should select a protective duration of exclusive breastfeeding for use in the Minnesota model.*

Response: NHDES assumed an exclusive breastfeeding duration of 12 months in its application of the MN model. This is a conservative assumption for the duration of exclusive breastfeeding based on recommendations of the American Academy of Pediatrics (AAP) and the World Health Organization (WHO). The U.S. Department of Health and Human Services, National Institute of Child Health and Human Development, notes that the AAP currently recommends:

> "…infants should be fed breast milk exclusively for the first 6 months after birth. Exclusive breastfeeding means that the infant does not receive any foods (except vitamin D) or fluid unless medically recommended. They further recommend that after the first 6 months and until the infant is 1-year-old, the mother continue breastfeeding while gradually introducing solid foods into the infant's diet." (AAP 2012; NIH 2018)

While experts recommend that infants transition from exclusive breastfeeding to a diet with complimentary foods after 6 months, NHDES determined that the assumption of a 12-month duration of exclusive breastfeeding in the model was conservative but appropriate given two considerations. The first is that NH-specific data from the CDC regarding breastfeeding duration indicates that a considerably higher proportion of NH infants are exclusively breastfed up to 6 months of age (30.2% of infants born in 2015; CDC 2018) when compared to the national average (24.9% of infants born in 2015). Additionally, there is an increasing trend of mothers who are or plan to breastfeed as indicated by the national data (CDC 2018). As infants are recommended to breastfeed up to 2 years of age, there is the possibility for additional exposure through breast milk which tends to contain higher concentrations of PFAS than the mother's drinking water. Secondly, the assumption of exclusive breastfeeding from 6 to 12 months of age is determined to be

appropriately protective given the mechanics of the model. Further discussion of this topic is found in Section IV of the June 2019 Report.

Comment: *NHDES should reconsider its selection of the relative source contribution (RSC) for each PFAS given available data from New Hampshire-specific and nationwide average blood concentrations of these four PFAS.*

Response: To derive the MCLs proposed in the final proposal, NHDES opted to apply a relative source contribution (RSC) of 50% for PFOA, PFOS, PFNA, and PFHxS (detailed explanation available in Section IV of the June 2019 Report). Based on the EPA Decision tree (EPA, 2000), NHDES capped the RSC from water at 50%, leaving up to 50% of the total safe exposure to come from non-drinking water sources. EPA recommends using average background concentrations for deriving RSCs, which in the case of PFAS can be estimated from the data collected by the National Health and Nutrition Examination Survey (NHANES). RSCs calculated using the average NHANES (2013-2014, as reported in Daly *et al.*, 2018) background serum levels for the ages 3 to 19 age group range from about 83 to 99% for the four PFAS, indicating background exposure only uses up 1 to 17% of the 50% allowed (See Table 4 in Section IV of the June 2019 Report). More recent data from NHANES suggest that the general background exposure rates are decreasing (CDC 2019). However, uncertainty about broader environmental contamination led NHDES to conclude that a 50% cap of the RSC was appropriate.

NHDES agrees that the use of New Hampshire-specific blood data potentially overestimates the background versus drinking water contributions of PFAS exposure. As these data were collected from communities with direct contamination of their drinking water supplies, their elevated serum levels likely have a significant portion that is due to drinking water or other potential sources (*e.g.*, dust deposition). Thus, NHDES used the NHANES estimates as calculations based on these populations potentially biases the resulting RSC estimate. However, these other environmental sources of exposure specific to these previously exposed populations underscores the necessity to cap the RSC at 50%.

Using an RSC of 50% for breastfed infants and the MN model, the predicted blood serum level for adult water consumers is approximately equal to or below 20% of the target serum threshold, or a 20% RSC for adults. See Section V of the June 2019 Report for the graphs of the estimated lifespan serum concentrations in relation to the RSC. These estimated serum levels are not predicted to result in a significant increase in serum PFAS levels relative to the national background levels. To achieve no increase above the national background levels would require setting standards at zero, which is inconsistent with standard setting procedures and at this time is not necessary to be adequately protective at all life stages.

Technical Comments Related to Health-Based Risk Assessment of PFOA

Comment: *NHDES did not select an appropriate critical health effect and principle study for deriving the PFOA reference dose, and subsequent MCL.*

Response: NHDES still recommends the use of hepatotoxicity (*i.e.*, liver enlargement and hypertrophy) as the critical health effect basis of the RfD for PFOA. This health effect endpoint is consistent with Health Canada (2016a) and the New Jersey Drinking Water Quality Institute (NJDWQI 2017). This is considered an adverse health outcome following chronic exposure to PFOA, and is relevant across all life stages and therefore appropriate for exposure modeling with the MN model. Additional information supporting this selection is detailed in the June 2019 Report.

NHDES disagrees with comments asserting that the hepatotoxic effects are irrelevant to human health based on the role of peroxisome proliferator-activated receptor α (PPARα) in rodent liver toxicity. As reviewed in the January 2019 Report and by other agencies (NHDES 2019; Health Canada 2016a; NJDWQI 2017; ATSDR 2018), there is evidence that the hepatic effects of PFOA are possibly mediated by PPARα-independent mechanisms and are therefore relevant to human health risk assessment. While humans are not susceptible to the same peroxisome proliferation observed in rodents, PPARα still plays a role in human lipid and energy metabolism, immune function and cell signaling (Issemann and Green, 1990; Lee *et al.*, 1995; Tyagi *et al.*, 2011).

NHDES does not agree that there is sufficient evidence to select the delayed mammary gland development in mice as the principal health effect for the PFOA RfD. Several comments criticized NHDES for not selecting this endpoint and assert that reports of any PFOA-related nuclear receptor activity (*e.g.*, PPARα, ERα or PR) from *in vitro* systems translates into human relevance of an effect from rodent models. NHDES considered the activations of PPARα and other nuclear receptors, and determined that there was insufficient information to rule out enhanced sensitivity in mice compared to humans as it relates to this specific outcome. As discussed in the January 2019 Report, this is due to interactions with nuclear receptor co-activators in mice (reviewed by Corton *et al.*, 2014) which have been shown to modulate PPARα-mediated effects on the development and function of mammary glands in mice (Qi *et al.*, 2004; Jia *et al.*, 2005). The functional significance remains unclear, as White *et al.* (2007) could not discern if effects on pups were due to changes in lactation or maternal toxicity other than the observed delays in mammary gland development. Direct investigation in a subsequent study failed to detect significant differences in treated mice (White *et al.*, 2011). Furthermore, no other state regulatory agency, to date, has adopted its use given uncertainty about its significance and the ATSDR which develops very conservative MRLs did not use this endpoint (ATSDR, 2018).

Epidemiological evidence associating this perinatal effect in mice to a human health outcome is limited to four studies. Three studies have suggested negative associations between certain PFAS (*i.e.*, PFOA and PFOS) to the duration of breastfeeding (Fei *et al.*, 2010; Romano *et al.*, 2016; Timmermann *et al.*, 2017), although two of these studies did not have information on prior breastfeeding durations which presents an important confounding factor (Fei *et al.*, 2010; Timmermann *et al.*, 2017). The most recent study accounting for prior breastfeeding, which several comments failed to reference, reported a positive association between PFAS and breastfeeding (Rosen *et al.*, 2018), although this outcome likely suggests an important role of PFAS toxicokinetics throughout pregnancy and breastfeeding. NHDES found that the epidemiological evidence for hepatotoxicity and altered lipid metabolism were more robust and deemed appropriate for use as the basis of an RfD at this time.

Conversely, other commenters criticized the selected critical health effect as being overly conservative given assessments made by another country (*i.e.*, Health Canada) and controlled studies of PFOA in humans. Health Canada (2016a) also selected hepatotoxicity as a critical effect for the basis of its RfD and concluded that increased liver weight at lower doses was relevant to human health. NHDES agreed with this judgement in critical effect selection. Health Canada opted for the no observed adverse effect level (NOAEL) for liver hypertrophy from Perkins *et al.* (2004) instead of Loveless *et al.* (2006). Health Canada (2016a) used a composite uncertainty factor of 25, whereas NHDES used 100 for PFOA. Health Canada uses values of 2.5 as partial and 10 for full uncertainty factors, whereas EPA methodology used 3 or 10, respectively. NHDES only differed from Health Canada in the more conservative application of a partial uncertainty factor for database uncertainty, which was not applied by Health Canada. Before the applications of uncertainty factors, the RfD proposed by NHDES is 610 ng/kg-d and the Health Canada value is 625 ng/kg-d. After uncertainty factors, the differences between the final drinking water values proposed by NHDES and Health Canada are therefore due to consideration of the relative source contribution (20% applied by Health Canada) and drinking water ingestion rate (*e.g.*, 1.5 L/d).

To the latter concern about over-conservatism from not deriving a RfD based on a recently-published clinical trial of PFOA (Convertino *et al.*, 2018), NHDES determined this study was not appropriate based on the population used. This study evaluated the direct effects of PFOA in late-stage cancer patients (n=49) and found negative associations with circulating cholesterol and free T_4 (Convertino *et al.*, 2018). Some commenters indicated that NHDES should re-evaluate this study and consider the effects observed in study participants who received a 6-week oral treatment of ammonium perfluorooctanoate. NHDES has serious reservations about relying on the results of such a study with a small sample size, restrictive inclusion criteria for participants, and the use of late-stage cancer patients whose metabolic function is not likely comparable to the general population. The age, health status, and limited information on population diversity of study participants raises several questions about confounding factors that were not addressed in the study's discussion.

Comment: NHDES did not select the appropriate uncertainty factors in its derivation of a reference dose for PFOA.

Response: NHDES applied uncertainty factors to each of the proposed RfDs after consideration of EPA methodology (EPA 2002) and RfD calculations made by other states agencies (NJDWQI 2017, 2018ab; MDH 2017, 2019ab; TCEQ 2016), the EPA (EPA 2016ab) and the ATSDR (2018). Section III of the June 2019 Report details each uncertainty factor applied for PFOA.

Evidence from gene knock-out (PPARα absent) studies indicates that other mechanisms of action are operating to cause liver toxicity besides those that are PPARα dependent. As the exact interaction of these mechanisms of toxicity with PPARα activation are still being studied, NHDES affirms that it is sound risk assessment policy to retain the partial uncertainty factor for animal-to-human toxicodynamic difference.

NHDES maintains the inclusion of the database uncertainty factor of 3 for immune and developmental effects is justified without being overly conservative. Per the National Toxicology Program (NTP)(2016), there is sufficient evidence for concern about PFOA's immunological effects as "PFOA is presumed to be an immune hazard to humans based on a high level of evidence that PFOA suppressed the antibody response from animal studies and a moderate level of evidence from studies in humans." This database uncertainty factor also accounts for other developmental effects (*e.g.*, delayed mammary gland development) that occur at lower doses in rodents but similar sensitivity in humans is currently suspect.

Technical Comments Related to Health-Based Risk Assessment of PFOS

Comment: NHDES did not select an appropriate critical health effect and principle study for deriving the PFOS reference dose, and subsequent MCL.

Response: NHDES agrees that in order to be more health protective the reference dose (RfD) calculation for PFOS should be based on immunosuppression. After review of available information, NHDES used the PFOS RfD recently proposed by MDH (2019a) and subsequent exposure assumptions, for immunosuppression as reported in Dong *et al.*, (2011).

As discussed in Section III of the June 2019 Report, NHDES selected the RfD developed by MDH (2019a) over the RfD for immunosuppression proposed by NJDWQI (2018a). MDH based the RfD for PFOS on reduced primary (IgM) antibody production in male mice following a 60-day oral exposure to PFOS (Dong *et al.*, 2011). Measurement of IgM is standard for immunotoxicity assays evaluating the T cell-dependent antibody response and, as a standard for regulatory toxicology (Ladics 2018, reviewed by DeWitt *et al.*, 2019), was deemed appropriate by NHDES. Results from this study were not amenable to benchmark dose modeling, so the NOAEL of 2,360 ng/mL (internal dose; Dong *et al.*, 2011) was used for RfD calculation. This RfD is on a similar order to others that have derived RfDs/MRLs for PFOS using immunosuppression as the base study or justification of additional uncertainty factors:

- ATSDR 2018 – 2.0 ng/kg-d (provisional, drinking water value varies)
- NJDWQI 2018a – 2.0 ng/kg-d (proposed MCL, 13 ng/L)
- MDH 2019a – 3.0 ng/kg-d (proposed health-based guidance value, 15 ng/L; recommended by NHDES)

As discussed by DeWitt *et al.* (2019), clinical classification of biomarkers of immune function plays a critical role in interpreting the existing epidemiological evidence. NHDES acknowledges some limitations of the human epidemiological data, as described by Chang *et al.* (2016), but determined that the growing body of evidence and consensus regarding the immunotoxicity of PFAS, including PFOS, merits use of immunosuppression in risk assessment. The National Toxicology Program (2016) concluded that PFOS is a presumed immunotoxin in humans, and emerging studies suggest that this is a relevant and sensitive endpoint for the protection of human health. More recently, ATSDR (2018) opted to apply additional uncertainty factors to arrive at an MRL that would be similar to an MRL or RfD based on immunosuppression.

Health Canada selected hepatotoxicity, similar to PFOA, as the critical health effect for PFOS (Health Canada, 2016). The proposed RfD based on liver toxicity (or hepatic hypertrophy) in rodents (Butenhoff *et*

al., 2012) was 60 ng/kg-d, after the application of a composite uncertainty factor of 25 (see previous PFOA RfD comment above). This was applied with a 20% relative source contribution and drinking water intake of 1.5 L/d to arrive at a drinking water value of 600 ng/L. Health Canada discussed the immunological studies on PFOS, but concluded that due to the nearly two-order of magnitude difference in lowest observed adverse effect levels (LOAELs) between various rodent studies this endpoint was not suitable for RfD development. NHDES concurs that the variation in LOAELs is a source of uncertainty, but given the significance of impaired immune function it is appropriate to use this endpoint to protect public health until more definitive scientific evidence quantifies the sensitivity of this outcome in humans.

Comment: *NHDES did not select the appropriate uncertainty factors in its derivation of a reference dose for PFOS.*

Response: NHDES applied uncertainty factors to each of the proposed RfDs after consideration of EPA methodology (EPA 2002) and RfD calculations made by other states agencies (NJDWQI 2017, 2018ab; MDH 2017, 2019ab; TCEQ 2016), the EPA (EPA 2016ab) and the ATSDR (2018). Section III of the June 2019 Report details each uncertainty factor applied for PFOS.

As the exact interaction of these mechanisms of immunotoxicity in rodents and humans is currently not understood, NHDES affirms that it is sound risk assessment policy to retain the partial uncertainty factor for animal-to-human toxicodynamic difference.

With respect to the database uncertainty factor, an additional partial database uncertainty factor of 3 was applied due to reports of thyroid disruption at early life stages (decreased T_4; as recommended by MDH 2019a). NHDES agrees with the approach taken by MDH, given the suggestive evidence for the human relevance of altered T_4 levels (reviewed by Ballesteros *et al.*, 2017 and ATSDR, 2018).

Technical Comments Related to Health-Based Risk Assessment of PFNA

Comment: *NHDES did not select an appropriate critical health effect and principle study for deriving the PFNA reference dose, and subsequent MCL.*

Response: As for the initial proposal, NHDES chose liver toxicity as the critical health effect basis of the RfD for PFNA. This used the benchmark dose model of Das *et al.* (2015) conducted by the NJDWQI (2018b). The LOAEL of this study was 12,400 ng/mL of serum PFNA (oral dose of 1 mg/kg-d), which was modeled down to 4,900 ng/mL as a basis for the RfD calculation. This study is the basis of the only other promulgated MCL, and NHDES determined there was sufficient evidence to support its application.

NHDES reviewed the recommended study on PFNA (Singh and Singh 2019). Singh and Singh (2019) evaluated the effects of PFNA on male Parkes mice following a 90-day exposure to either 0.2 or 0.5 mg/kg-d. For several of the evaluated outcomes, including reduced litter size, infertility, and histological changes in the testes of exposed mice, the no observed adverse effect level was 0.2 mg/kg-d.

Singh and Singh (2019) did not report internal serum doses for PFNA at any stage of the 90-day exposure, which makes direct comparisons to the internal doses reported by Das *et al.* (2015) unfeasible as there is limited toxicokinetic information on PFNA in this strain. Furthermore, this limits consideration of benchmark dose modeling for this endpoint given the importance of internal versus external doses. A single-dose (1 or 10 mg/kg) study using CD-1 mice suggests that the serum half-life of PFNA ranges from 34-69 days in males and 26-68 days in females (Tatum-Gibbs *et al.* 2011). This half-life is longer than the exposure and it is unclear what the internal steady-state levels would be in mice throughout the 90-day exposure.

One other study provides some estimate of internal serum levels at the NOAEL reported by Singh and Singh (2019). Using male Balb/c mice, Wang *et al.* (2015) measured serum levels of PFNA to be approximately 11,500 ng/mL at the LOAEL for hepatic hypertrophy following a 14-day exposure. The oral dose (0.2 mg/kg-d) for this LOAEL in Wang *et al.* (2015) was identical to the NOAEL for reduced litter size, infertility, and histological changes in the testes identified at the end of a 90-day exposure (Singh and Singh 2019). Given these dosing similarities between the two mouse studies (Wang *et al.*, 2015; Singh and Singh 2019) and the predicted serum levels in the proposed MCL, NHDES believes the present reference

dose combined with the exposure assumptions provide a protective margin of exposure for the aforementioned health effects.

Comment: NHDES did not select the appropriate uncertainty factors in its derivation of a reference dose for PFNA.

Response: NHDES applied uncertainty factors to each of the proposed RfDs after consideration of EPA methodology (EPA 2002) and RfD calculations made by other states agencies (NJDWQI 2017, 2018ab; MDH 2017, 2019ab; TCEQ 2016), the EPA (EPA 2016ab) and the ATSDR (2018). Section III of the June 2019 Report details each uncertainty factor applied for PFNA.

Similar to PFOA, evidence from gene knock-out (PPARα absent) studies has indicated that other mechanisms of action are operating to cause liver toxicity besides those that are PPARα dependent. As the exact interaction of these mechanisms of toxicity with PPARα activation are still being studied, NHDES affirms that it is sound risk assessment policy to retain the partial uncertainty factor for animal-to-human toxicodynamic difference.

As summarized in Section III of the June 2019 Report, NHDES did not agree with the additional application of uncertainty factors for duration of exposure. NHDES used the more conservative half-life estimate of PFNA derived from men and older women (4.3 years; Zhang *et al.*, 2013). Given the application of this more conservative half-life estimate, NHDES removed the associated partial database database uncertainty factor for PFNA. NHDES retained the partial database uncertainty factor of 3 to account for a lack of multigenerational rodent studies using PFNA, as well as concern for potential immunotoxic impacts seen with other PFAS, such as PFOA (NTP 2016; DeWitt *et al.*, 2012, 2019).

Technical Comments Related to Health-Based Risk Assessment of PFHxS

Comment: NHDES did not select an appropriate critical health effect and principle study for deriving the PFHxS reference dose, and subsequent MCL.

Response: NHDES disagrees with the comment that a different critical health effect should have been selected for PFHxS. Compared to PFOA, PFOS, and PFNA, there are significantly fewer studies available for understanding the health effects of PFHxS and its toxicity in rodent models. This is especially concerning given the dramatically longer half-life estimates for PFHxS despite the fact that it possesses a shorter carbon chain in comparison to PFNA, PFOA, and PFOS. Thus, there is significant concern for the health impacts of chronic exposure but an absence of long-term exposure studies in rodents. While liver toxicity and altered cholesterol metabolism are consistent with effects reported in association with other PFAS, the limited dataset for this compound merits consideration of any changes in an apical outcome such as reduced litter size. ATSDR did not review this study as a part of their 2018 draft toxicological profile for perfluoroalkyls (ATSDR 2018), but NHDES found that the statistically significant reduction in litter size, alteration in genital development in pups, and other observed toxicities merited consideration as mice may be better models than rats for evaluating PFHxS.

NHDES selected a reduced litter size as the critical health effect, based on results from mice orally-exposed to PFHxS for a sub-chronic duration prior to gestation (Chang *et al.*, 2018). Section III of the June 2019 Report provides additional information on this decision. A detailed review of background studies and RfD calculations based on this endpoint is currently under external peer-review for publication (Ali *et al.*, under review).

NHDES agreed that the volume of distribution should reflect the critical health effect in this case, and applied the female volume of distribution (213 mL/kg-d; Sundström *et al.*, 2012) for reference dose calculation. Details on its application are described in Section III of the June 2019 Report.

Comment: NHDES should evaluate the use of benchmark dose modeling instead of the no-observed-adverse-effect-level (NOAEL) for the critical health effect of reduced litter size in mice.

Response: In collaboration with faculty at the University of Florida, NHDES developed a RfD for PFHxS based on benchmark dose modeling of data reported in Chang *et al.* (2018). The supporting decisions and

methodology are currently under peer-review for publication, and the detailed methodology and numeric outputs will be made available after a decision is made regarding this publication.

Comment: NHDES did not select the appropriate uncertainty factors in its derivation of a reference dose for PFHxS.

Response: NHDES applied uncertainty factors to each of the proposed RfDs after consideration of EPA methodology (EPA 2002) and RfD calculations made by other states agencies (NJDWQI 2017, 2018ab; MDH 2017, 2019ab; TCEQ 2016), the EPA (EPA 2016ab) and the ATSDR (2018). Section III of the June 2019 Report details each uncertainty factor applied for PFHxS.

After review of this comment and applications of the database uncertainty factor, NHDES agreed that a partial database uncertainty factor of 3 was more appropriate. However, NHDES also identified studies suggesting that longer exposure durations would have been more appropriate for evaluating PFHxS given reproductive effects seen with PFOS (Feng *et al.*, 2015) and the considerably long half-life of PFHxS in humans (Olsen *et al.*, 2007; Li *et al.*, 2018). The rationale behind these decisions is detailed in Section III of the June 2019 Report.

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2018. Toxicological Profile for Perfluoroalkyls – Draft for Public Comment, June 2018. Accessed online at: https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf.

Agency for Toxic Substances and Disease Registry (ATSDR). 2018a. Minimal Risk Levels (MRLs) – For Professionals. Retrieved from https://www.atsdr.cdc.gov/mrls/index.asp.

Agency for Toxic Substances and Disease Registry (ATSDR). 2019. Public Comment Version Per and Polyfluoroalkyl Substances (PFAS) in the Pease Tradeport Public Water System. EPA PWS ID: 1951020.

Ali JM, Roberts SM, Gordon DS, Stuchal LD. (under review) Derivation of a chronic reference dose for perfluorohexane sulfonate (PFHxS) for reproductive toxicity in mice.

American Academy of Pediatrics. (2012). Breastfeeding and the use of human milk. *Pediatrics, 129(3)*, e827–e841. Retrieved from http://pediatrics.aappublications.org/content/129/3/e827.full.pdf+html

Ballesteros V, Costa O, Iñiguez C, Fletcher T, Ballester F, Lopez-Espinosa MJ. 2017. Exposure to perfluoroalkyl substances and thyroid function in pregnant women and children: A systematic review of epidemiologic studies. Environ Int, 99:15-28. doi: 10.1016/j.envint.2016.10.015.

Bartell SM, Calafat AM, Lyu C, *et al.* 2010. Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. Environ Health Perspect 118(2):222-228.

Butenhoff JL, Chang SC, Olsen GW, *et al.* 2012. Chronic dietary toxicity and carcinogenicity study with potassium perfluorooctanesulfonate in Sprague Dawley rats. Toxicology 293(1-3):1-15.

Centers for Disease Control and Prevention (CDC). (2018). Breastfeeding Report Card. Retrieved from https://www.cdc.gov/breastfeeding/data/reportcard.htm.

Centers for Disease Control and Prevention (CDC). (2019). Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, January 2019, Volume One. Retrieved from https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Jan2019-508.pdf.

Chang ET, Adami HO, Boffetta P, Wedner HJ, Mandel JS. 2016. A critical review of perfluorooctanoate and perfluorooctanesulfonate exposure and immunological health conditions in humans. Crit Rev Toxicol., 46(4): 279-331.

Chang S, Butenhoff JL, Parker GA, Coder PS, Zitzow JD, Krisko RM, Bjork JA, Wallace KB, Seed JG. 2018. Reproductive and developmental toxicity of potassium perfluorohexanesulfonate in CD-1 mice. Reproductive Toxicology 78: 150-168.

Convertino M, *et al.* 2018. Stochastic Pharmacokinetic-Pharmacodynamic Modeling for Assessing the Systemic Health Risk of Perfluorooctanoate (PFOA). Toxicological Sciences 163(1): 293-306.

Corton JC, Cunningham ML, Hummer BT, *et al.* 2014. Mode of action framework analysis for receptor-mediated toxicity: The peroxisome proliferator-activated receptor alpha (PPARα) as a case study. Crit Rev Toxicol 4444(1):1-49. 10.3109/10408444.2013.835784.

Daly ER, Chan BP, Talbot EA, Nassif J, Bean C, Cavallo SJ, Metcalf E, Simone K, Woolf AD. 2018. Per- and polyfluoroalkyl substance (PFAS) exposure assessment in a community exposed to contaminated drinking water, New Hampshire, 2015. Int J Hyg Environ Health. 221(3):569-577. doi: 10.1016/j.ijheh.2018.02.007.

Das KP, Grey BE, Rosen MB, *et al.* 2015. Developmental toxicity of perfluorononanoic acid in mice. Reprod Toxicol 51:133-144. 10.1016/j.reprotox.2014.12.012.

DeWitt JC, Blossom SJ, Schaider LA. 2019. Exposure to per-fluoroalkyl and polyfluoroalkyl substances leads to immunotoxicity: epidemiological and toxicological evidence. J Expo Sci Environ Epidemiol. 29(2):148-156. doi: 10.1038/s41370-018-0097-y.

DeWitt JC, Peden-Adams MM, Keller JM, Germolec DR. 2012. Immunotoxicity of Perfluorinated Compounds: Recent Developments. Toxicologic Pathology, 40: 300-311.

Dhingra R, Winquist A, Darrow LA, Klein M, Steenland K. 2017. A study of reverse causation: examining the associations of perfluorooctanoic acid serum levels with two outcomes. Environ Health Perspect 125:416-421; https://ehp.niehs.nih.gov/doi/10.1289/EHP273.

Dong GH, Liu MM, Wang D, *et al.* 2011. Sub-chronic effect of perfluorooctanesulfonate (PFOS) on the balance of type 1 and type 2 cytokine in adult C57BL6 mice. Arch Toxicol 85(10):1235-1244.

Dong GH, Zhang YH, Zheng L, *et al.* 2009. Chronic effects of perfluorooctanesulfonate exposure on immunotoxicity in adult male C57BL/6 mice. Arch Toxicol 83(9):805-815.

Ernst A, Brix N, Lauridsen LLB, Olsen J, Parner ET, Liew Z, Olsen LH, Ramlau-Hansen CH. 2019. Exposure to Perfluoroalkyl Substances during Fetal Life and Pubertal Development in Boys and Girls from the Danish National Birth Cohort. Environ Health Perspect. 127(1):17004. doi: 10.1289/EHP3567.

Fei C, McLaughlin JK, Lipworth L, Olsen J. 2010. Maternal concentrations of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) and duration of breastfeeding. Scand J Work Environ Health. 36(5):413–21.

Feng X, Wang X, Cao X, Xia Y, Zhou R, Chen L. 2015. Chronic Exposure of Female Mice to an Environmental Level of Perfluorooctane Sulfonate Suppresses Estrogen Synthesis Through Reduced Histone H3K14 Acetylation of the StAR Promoter Leading to Deficits in Follicular Development and Ovulation. Toxicol Sci. 148(2):368-79. doi: 10.1093/toxsci/kfv197.

Frisbee SJ, Brooks AP Jr, Maher A, Flensborg P, Arnold S, Fletcher T, Steenland K, Shankar A, Knox SS, Pollard C, Halverson JA, Vieira VM, Jin C, Leyden KM, Ducatman AM. 2009. The C8 health project: design, methods, and participants. Environ Health Perspect. 117(12):1873-82. doi: 10.1289/ehp.0800379.

Goeden HM, Greene CW, Jacobus JA. 2019. A transgenerational toxicokinetic model and its use in derivation of Minnesota PFOA water guidance. J Expo Sci Environ Epidemiol. 29(2):183-195. doi: 10.1038/s41370-018-0110-5.

Health Canada. 2016a. Perfluorooctanoic acid (PFOA) in drinking water. Retrieved from https://www.canada.ca/content/dam/hc-sc/healthy-canadians/migration/health-system-systeme-sante/consultations/acide-perfluorooctanoic-acid/alt/perfluorooctanoic-eng.pdf.

Health Canada. 2016. Perflurooctane sulfonate (PFOS) in drinking water. Retrieved from https://www.canada.ca/content/dam/hc-sc/healthy-canadians/migration/health-system-systeme-sante/consultations/perfluorooctane-sulfonate/alt/perfluorooctane-sulfonate-eng.pdf.

Issemann I, Green S. 1990. Activation of a member of a steroid hormone receptor superfamily by peroxisome proliferators. Nature, 347:645-650.

Jia, Y., Qi, C., Zhang, Z., Zhu, Y. T., Rao, S. M., and Zhu, Y. J. (2005). Peroxisome proliferator-activated receptor-binding protein null mutation results in defective mammary gland development. J. Biol. Chem. 280, 10766–10773.

Ladics G.S. 2018. The Sheep Erythrocyte T-Dependent Antibody Response (TDAR). In: DeWitt J., Rockwell C., Bowman C. (eds) Immunotoxicity Testing. Methods in Molecular Biology, vol 1803. Humana Press, New York, NY.

Lee SS-T, Pineau T, Drago J, Lee EJ, Owens JW, Kroetz DL, Fernandez-Salguero PM, Westphal H, and Gonzalez FJ (1995) Targeted disruption of the alpha isoform of the peroxisome proliferator-activated receptor gene in mice results in abolishment of the pleiotropic effects of peroxisome proliferators. Mol Cell Biol 15:3012–3022.

Li Y, Fletcher T, Mucs D, *et al.* 2018. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occup Environ Med 75(1):46-51. 10.1136/oemed-2017-104651.

Loccisano AE, *et al.* 2013. Development of PBPK Models for PFOA and PFOS for Human Pregnancy and Lactation Life Stages. J Toxicol Environ Health A. 76(1): 25-57.

Loveless SE, Finlay C, Everds NE, *et al.* 2006. Comparative responses of rats and mice exposed to linear/branched, linear, or branched ammonium perfluorooctanoate (APFO). Toxicology 220:203-217.

Michigan Department of Health and Human Services (MIDHHS). 2019. Public health drinking water screening levels for PFAS. Retrieved from https://www.michigan.gov/documents/pfasresponse/MDHHS_Public_Health_Drinking_Water_Screening_Levels_for_PFAS_651683_7.pdf.

Michigan PFAS Science Advisory Panel Report. 2018. Scientific Evidence and Recommendations for Managing PFAS Contamination in Michigan. December 7, 2018. Retrieved from https://www.michigan.gov/documents/pfasresponse/Science_Advisory_Board_Report_641294_7.pdf.

Minnesota Department of Health (MDH). 2017a. Background Document. Toxicokinetic Model for Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoic Acid (PFOA) and Its Use in the Derivation of Human Health-Based Water Guidance Values.

Minnesota Department of Health (MDH). 2017 - Toxicological Summary for: Perfluorooctanoate. Retrieved from http://www.health.state.mn.us/divs/eh/risk/guidance/gw/pfoa.pdf.

Minnesota Department of Health (MDH). 2019b - Toxicological Summary for: Perfluorohexane sulfonate. Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfhxs.pdf.

Minnesota Department of Health (MDH). 2019a - Toxicological Summary for: Perfluorooctane sulfonate. Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfos.pdf.

National Institutes of Health (NIH). (2018). What are the recommendations for breastfeeding? Retrieved from https://www.nichd.nih.gov/health/topics/breastfeeding/conditioninfo/recommendations.

National Toxicology Program (NTP). 2016. NTP Monograph: Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid or Perfluorooctane Sulfonate. September 2016. Retrieved from https://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/pfoa_pfosmonograph_508.pdf.

New Jersey Drinking Water Quality Institute (NJDWQI). 2017. Health-Based Maximum Contaminant Level Support Document: Perfluorooctanoic Acid (PFOA). February 15, 2017. Retrieved from https://www.state.nj.us/dep/watersupply/pdf/pfoa-appendixa.pdf.

New Jersey Drinking Water Quality Institute (NJDWQI). 2018a. Health-Based Maximum Contaminant Level Support Document: Perfluorooctane Sulfonate (PFOS). June 5, 2018. Retrieved from https://www.state.nj.us/dep/watersupply/pdf/pfos-recommendation-appendix-a.pdf.

New Jersey Drinking Water Quality Institute (NJDWQI). 2018b. Health-Based Maximum Contaminant Level Support Document: Perfluorononanoic Acid (PFNA). Retrieved from https://www.state.nj.us/dep/watersupply/pdf/pfna-health-effects.pdf.

NHDES. 2019. January 2019 Report. Retrieved from https://www.des.nh.gov/organization/commissioner/pip/publications/documents/r-wd-19-01.pdf.

NJ DEP SRP. 2019. New Jersey Department of Environmental Protection Site Remediation Program – Contaminants of Emerging Concern. Retrieved from https://www.nj.gov/dep/srp/emerging-contaminants/.

Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, Zobel LR. 2007. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect 115:1298-1305.

Olsen J, Melbye M, Olsen SF, Sorensen TI, Aaby P, Andersen AM, *et al.* 2001. The Danish National Birth Cohort–its background, structure and aim. Scand J Public Health 29(4):300–307, PMID: 11775787, 10.1177/14034948010290040201.

Perkins RG, Butenhoff JL, Kennedy GL, *et al.* 2004. 13-Week dietary toxicity study of ammonium perfluorooctanoate (APFO) in male rats. Drug Chem Toxicol 27(4):361-378.

Qi, C., Kashireddy, P., Zhu, Y. T., Rao, S. M., and Zhu, Y. J. (2004). Null mutation of peroxisome proliferator-activated receptor-interacting protein in mammary glands causes defective mammopoiesis. J. Biol. Chem. 279, 33696–33701.

Romano ME, Xu Y, Calafat AM, Yolton K, Chen A, Webster GM, Eliot MN, Howard CR, Lanphear BP, Braun JM. 2016. Maternal serum perfluoroalkyl substances during pregnancy and duration of breastfeeding. Environ Res. 149:239–46.

Rosen EM, Brantsæter AL, Carroll R, Haug L, Singer AB, Zhao S, Ferguson KK. 2018. Maternal Plasma Concentrations of Per- and polyfluoroalkyl Substances and Breastfeeding Duration in the Norwegian Mother and Child Cohort. Environ Epidemiol. 2(3). pii: e027. doi: 10.1097/EE9.0000000000000027.

Singh S, Singh SK. 2019. Chronic exposure to perfluorononanoic acid impairs spermatogenesis, steroidogenesis and fertility in male mice. J Appl Toxicol. 39(3):420-431. doi: 10.1002/jat.3733.

Sundström M, Chang SC, Noker PE, Gorman GS, Hart JA, Ehresman DJ, Bergman Å, Butenhoff JL. 2012. Comparative pharmacokinetics of perfluorohexanesulfonate (PFHxS) in rats, mice, and monkeys. Reproductive Toxicology 33(4):441-451.

Tatum-Gibbs K, Wambaugh JF, Das KP, *et al.* 2011. Comparative pharmacokinetics of perfluorononanoic acid in rat and mouse. Toxicology 281(1-3):48-55. 10.1016/j.tox.2011.01.003.

Texas Commission on Environmental Quality (TCEQ) technical Document on Perfluoro Compounds (PFCs). 2016. Retrieved from: https://www.tceq.texas.gov/assets/public/implementation/tox/evaluations/pfcs.pdf.

Timmermann CAG, Budtz-Jorgensen E, Petersen MS, Weihe P, Steuerwald U, Nielsen F, Jensen TK, Grandjean P. 2017. Shorter duration of breastfeeding at elevated exposures to perfluoroalkyl substances. Reproductive Toxicology. 68:164–70. Epub 2016/07/17. DOI: 10.1016/j.reprotox.2016.07.010.

Tyagi S, Gupta P, Saini AS, Kaushal C, and Sharma S. 2011. The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. J Adv Pharm Technol Res. 2(4): 236–240.

U.S. Environmental Protection Agency (EPA). 2000. Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000) Documents. Accessed April 2019. Retrieved from https://www.epa.gov/wqc/methodology-deriving-ambient-water-quality-criteria-protection-human-health-2000-documents.

U.S. Environmental Protection Agency (EPA). 2002. A Review of the Reference Dose and Reference Concentration Processes. EPA/630/P-02/0002F. Risk Assessment Forum, Washington, DC. Retrieved from https://www.epa.gov/osa/review-reference-dose-and-reference-concentrationprocesses.

U.S. Environmental Protection Agency (EPA). 2006. SAB Review of EPA's Draft Risk Assessment of the Potential Human Health Effects Associated with PFOA and Its Salts. SAB06006.

U.S. Environmental Protection Agency (EPA). 2011. Exposure Factors Handbook: 2011 Edition. EPA/600/R-090/052F. Office of Research and Development, National Center for Environmental Assessment, Washington, D.C. 1436 pp. Accessed online at: https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252.

U.S. Environmental Protection Agency (EPA). 2016a. Health Effects Support Document for Perfluorooctanoic acid (PFOA). Document # EPA 822-R-16-003. May 2016. Retrieved from https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_hesd_final_508.pdf.

U.S. Environmental Protection Agency (EPA). 2016b. Health Effects Support Document for Perfluorooctane Sulfonate (PFOS). Document # EPA 822-R-16-002. May 2016. Retrieved from https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf.

U.S. EPA. 2018. National Primary Drinking Water Regulations. Retrieved from https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations#one.

U.S. Environmental Protection Agency (EPA). 2019. Exposure Factors Handbook: Chapter 3 Update. Office of Research and Development, National Center for Environmental Assessment, Washington, D.C. 1436 pp. Accessed online at: https://www.epa.gov/sites/production/files/2019-02/documents/efh_-_chapter_3_update.pdf.

Wang, J, Yan, S, Zhang, W, Zhang, H, Dai, J. 2015. Integrated proteomic and miRNA transcriptional analysis reveals the hepatotoxicity mechanism of PFNA exposure in mice. J Proteome Res. 14:330-41.

White SS, Calafat AM, Kuklenyik Z, *et al.* 2007. Gestational PFOA exposure of mice is associated with altered mammary gland development in dams and female offspring. Toxicol Sci 96(1):133-144.

White SS, Stanko JP, Kato K, *et al.* 2011. Gestational and chronic low-dose PFOA exposures and mammary gland growth and differentiation in three generations of CD-1 mice. Environ Health Perspect 119(8):1070-1076.

Winquist A, Lally C, Shin HM, Steenland K. 2013. Design, methods, and population for a study of PFOA health effects among highly exposed mid-Ohio valley community residents and workers. Environ Health Perspect. 121(8):893-9. doi: 10.1289/ehp.1206450.

Zhang Y, Beesoon S, Zhu L, *et al.* 2013. Biomonitoring of perfluoroalkyl acids in human urine and estimates of biological half-life. Environ Sci Technol 47(18):10619-10627. 10.1021/es401905e.

Attachment 1: "New Hampshire Department of Environmental Services Technical Background for the June 2019 Proposed Maximum Contaminant Levels (MCLs) for Perfluorooctane sulfonic Acid (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorononanoic Acid (PFNA), and Perfluorohexane sulfonic Acid (PFHxS)" and findings of a peer review of NHDES's derivations conducted by Stephen M. Roberts, Ph.D.

Attachment 2: NHDES updated cost and benefit considerations

Attachment 3: NHDOJ letter

ATTACHMENT 1

New Hampshire Department of Environmental Services

Technical Background Report for the June 2019 Proposed Maximum Contaminant Levels (MCLs) and Ambient Groundwater Quality Standards (AGQSs) for Perfluorooctane sulfonic Acid (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorononanoic Acid (PFNA), and Perfluorohexane sulfonic Acid (PFHxS)

And

Letter from Dr. Stephen M. Roberts, Ph.D. dated 6/25/2019 – Findings of Peer Review Conducted on Technical Background Report

June 28, 2019

New Hampshire Department of Environmental Services

Technical Background Report for the June 2019 Proposed Maximum Contaminant Levels (MCLs) and Ambient Groundwater Quality Standards (AGQSs) for Perfluorooctane sulfonic Acid (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorononanoic Acid (PFNA), and Perfluorohexane sulfonic Acid (PFHxS)

June 28, 2019

Table of Contents

Abbreviations

AFFF - aqueous film forming foam

AGQS - Ambient Groundwater Quality Standard

APFO – ammonium perfluorooctanoate

ATSDR – Agency for Toxic Substances and Disease Registry

BMD – benchmark dose

BMDL – benchmark dose lower-bound confidence limit

C8 – an alternative name for perfluorooctanoic acid

CAR – constitutive androstane receptor

CAS# - Chemical Abstracts Service Registry Number

CDC – Centers for Disease Control and Prevention

CSF – cancer slope factor

d - day

DAF – dosimetric adjustment factor

IR – ingestion rate

IRIS - Integrated Risk Information System

kg - kilogram

L - liter

LHA – lifetime health advisory

Ln – natural logarithm

LOAEL – lowest observed adverse effect level

MCL – maximum contaminant level

mg - milligram

MDH – Minnesota Department of Health

MRL – minimal risk level

ng - nanogram

NHDES – New Hampshire Department of Environmental Services

NH DHHS – New Hampshire Department of Health & Human Services

NIS - National Immunization Survey

NJDWQI – New Jersey Drinking Water Quality Institute

NOAEL – no observed adverse effect level

NTP – National Toxicology Program

PFAS – perfluoroalkyl substances

PFHxS – perfluorohexane sulfonic acid

PFNA – perfluorononanoic acid

PFOA – perfluorooctanoic acid

PFOS – perfluorooctane sulfonic acid

POD – point of departure

PPAR - peroxisome proliferator-activated receptor

ppb –parts-per-billion

ppt – parts-per-trillion

RME – reasonable maximum exposure

RSC – relative source contribution

$t_{1/2}$ – half-life

UF – uncertainty factor

USEPA – U.S. Environmental Protection Agency

V_d – volume of distribution

WHO – World Health Organization

α – alpha, used to denote specific subtypes of biological molecules (i.e., proteins)

β – beta, used to denote specific subtypes of biological molecules (i.e., proteins)

γ - gamma, used to denote specific subtypes of biological molecules (i.e., proteins)

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New Hampshire Department of Environmental Services would like to thank the numerous New Hampshire stakeholders and residents who provided valuable technical commentary on the initially proposed MCLs for PFOA, PFOS, PFNA and PFHxS. This includes New Hampshire's residents, academic institutions, community advocacy groups, representatives for the business community and municipalities. The science followed in deriving the currently proposed maximum contaminant levels was enacted in part as a result of their contributions. Additionally, NHDES is grateful for insights and information shared by professionals from other state agencies, interstate collaborative working groups and professional societies.

Section I. Executive Summary

The objective of the health-based risk assessment was identifying drinking water concentrations of perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA) and perfluorohexane sulfonic acid (PFHxS) that provide adequate protection of human health at all life stages, including but not limited to pre-natal development. This document provides the technical basis for the proposed maximum contaminant levels (MCLs,) which by law become Ambient Groundwater Quality Standards (AGQSs), following evaluation of technical comments submitted up to April 12th, 2019, public comment deadline, as well as peer-reviewed scientific literature published since January 1st, 2019, and external review by Dr. Stephen Roberts at the University of Florida. As a result of this process, NHDES is proposing the following maximum contaminant levels (MCLs):

- **12 ng/L for Perfluorooctanoic acid, or perfluorooctanoate (PFOA)**
- **15 ng/L for Perfluorooctane sulfonic acid, or perfluorooctane sulfonate (PFOS)**
- **11 ng/L for Perfluorononanoic acid, or perfluorononanoate (PFNA)**
- **18 ng/L for Perfluorohexane sulfonic acid, or perfluorohexane sulfonate (PFHxS)**

These health-based values are intended as health-protective limits against the chronic health effects for a through-life exposure. The primary associated health outcomes are hepatotoxicity and changes in lipid metabolism (PFOA and PFNA), suppressed immune response to vaccines (PFOS) and impaired female fertility (PFHxS). Secondary associated health effects that are expected to be less sensitive are changes in thyroid and sex hormone levels, early-life growth delays, changes in cholesterol levels and biomarkers of liver function, neurobehavioral effects, and a possible risk for certain cancers (i.e., testicular and kidney cancer).

These proposed MCLs are lower than those proposed in January 2019 (NHDES 2019) as a result of new studies and models that indicate the standards need to be lower to be adequately protective of health at all life stages. Specifically, a peer reviewed toxicokinetic model was published by the Minnesota Department of Health (Goeden et al., 2019) that predicts blood serum levels across a lifetime. Using similar studies as those from the initial proposal and those suggested in technical comments submitted by April 12th, 2019, this model indicates lower standards are necessary to avoid unacceptable elevations in the serum levels of breastfed infants and children who were breastfed as infants.

The technical basis for the proposed MCLs is detailed in Sections III and IV, and the modeling results and conclusions are presented in Section V. Briefly, this risk assessment utilized upper value, “conservative” estimates regarding: daily water consumption rates throughout life, breastmilk consumption rates through infancy, the duration of exclusive breastfeeding (12 months), relative source contribution, absorption efficiency and consideration of breastmilk transfer. Central tendency, or less conservative, assumptions included: use of uncertainty factors, human half-life estimates, placental and breastmilk transfer efficiencies of PFAS, and the recommendation of individual MCLs instead of assuming toxicological equivalency among the four PFAS evaluated.

The health effects of PFAS is an evolving area of research and it is expected that future research will improve our understanding of the quantitative risks associated with PFAS. This may result in higher or lower recommendations for these and other PFAS in the future. NHDES is committed to reviewing new scientific information on PFAS to improve the understanding of this large group of chemicals and making future recommendations for evidence-based health protective drinking water standards.

Section II. Introduction

Perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorohexanesulfonic acid (PFHxS) are individual compounds in a large class of chemicals known as perfluorinated compounds (PFCs) and more broadly as per- and polyfluoroalkyl substances (PFAS). They have been widely used since the 1940s in commercial, industrial, and household products and applications, including production of water, grease, and stain-resistant materials, fire suppression foams, non-stick cookware, wax removers, etc. (ATSDR 2018b).

All four compounds have been detected in New Hampshire's groundwater and surface water. Their widespread use, persistence and mobility in the environment and bioaccumulative properties has resulted in the detection of PFAS in blood serum in humans and animals worldwide. This has led to considerable research into their toxicity and health effects. The health effects associated with PFAS exposure are currently being researched extensively by toxicologists and epidemiologists worldwide, resulting in numerous publications being released on a continuous basis.

According to the Agency for Toxic Substances and Disease Registry (ATSDR)(ATSDR 2018b) the following health impacts may be associated with PFAS (specific compounds as noted by ATSDR):

- Hepatotoxicity - changes in certain liver enzymes in serum (PFOA, PFOS, PFHxS)
- Increases in total and LDL cholesterol levels (PFOA, PFOS, PFNA)
- Small decreases in birth weight (PFOA, PFOS)
- Endocrine system effects (PFOA, PFOS)
- Reproductive toxicity - decreased fertility (PFOA, PFOS)
- Immunotoxicity - decreased vaccine response (PFOA, PFOS, PFHxS)
- Suggestive evidence of carcinogenicity, specifically testicular and kidney cancer (PFOA, PFOS)
- Suggestive evidence of association with pregnancy-induced hypertension and/or pre-eclampsia (PFOA, PFOS)

For additional information on the toxicity and health effects of these compounds, please visit the ATSDR webpage at: https://www.atsdr.cdc.gov/pfas/health-effects.html

In addition to the ATSDR draft toxicological profile on perfluoroalkyls, several other state (NJDWQI 2017, 2018ab; MDH 2018, 2019ab; MI PFAS Science Advisory Panel 2018), federal (EPA 2016ab; NTP 2016) and international agencies (IARC 2016; Health Canada 2016ab; EFSA 2018) have reviewed the toxicological data related to PFAS and identified similar associated health impacts.

This document presents the health-based risk assessment that derived the proposed MCLs and Ambient Groundwater Quality Standards (AGQS) for these four compounds. In January 2019, NHDES released its initially proposed MCLs along with a supporting document that explained the rationale used and scientific literature reviewed to arrive at its recommendation (NHDES, 2019). The current report is not an exhaustive review of all existing studies that reference PFOA, PFOS, PFNA, PFHxS or other PFAS; rather, it is an update to the previous assessment after evaluation of newer studies and technical comments since the initial MCL proposal in January 2019 (NHDES, 2019).

Section III. Reference Dose Derivation

The U.S. EPA (2002) defines a reference dose (RfD) as:

> "An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime."

For PFAS, a RfD can be expressed in units of nanograms of specified PFAS (ng), per kilogram of a person's body weight (kg), per day (ng/kg-d). This allows for estimation of chemical-specific daily doses that are readily scaled to persons of differing sizes. A RfD is not the same as the minimal risk levels (MRLs) developed and used by ATSDR in that 1) MRLs are not developed with the same considerations as RfDs, and 2) MRLs are not used to define action or clean up levels for chemical contaminants (EPA 2002; ATSDR 2018a). NHDES derived RfDs for PFOA, PFOS, PFNA and PFHxS (Table 1). *Additionally, it is important to note that a RfD is a population-level value and its associated blood concentration is not considered a clinically-relevant value for individuals.*

Table 1. Summary of RfDs and MCLs.

Compound	Reference dose (RfD)	Exposure Assumptions	Maximum Contaminant Level (MCL)
Perfluorooctanoic acid (PFOA)	6.1 ng/kg-d	See Section IV	12 ng/L
Perfluorooctanesulfonic acid (PFOS)	3.0 ng/kg-d	See Section IV	15 ng/L
Perfluorononanoic acid (PFNA)	4.3 ng/kg-d	See Section IV	11 ng/L
Perfluorohexanesulfonic acid (PFHxS)	4.0 ng/kg-d	See Section IV	18 ng/L

Derivation of a RfD requires selection of three components (Equation 2): a point of departure (POD), uncertainty factors (UF) and, where appropriate, a dosimetric adjustment factor (DAF). The POD is based on a sensitive and human-relevant critical health effect from either animal or human studies. For PFAS, this is typically a blood concentration of a certain compound at which there is no observable adverse effect in animals (e.g. rodents). As rodents are not humans, the UF is applied to be protective by reducing the animal POD to a lower and acceptable human target serum level. The DAF then converts, by estimation, the blood concentration (ng/mL) to a body weight-adjusted (kg) amount of the chemical (ng) external to the body that would need to be ingested on a daily basis to reach the human target serum level.

$$\text{Reference dose (ng/kg/d)} = \frac{\text{Point of departure (ng/mL)}}{\text{Total uncertainty factors (unitless)}} \times \text{Dosimetric adjustment factor (mL/kg/d)}$$

As the EPA RfDs for PFOA and PFOS were deemed insufficiently protective, and there are no values for PFNA or PFHxS in the EPA Integrated Risk Information System (IRIS) database, NHDES evaluated the RfDs proposed by other agencies and derived its own values. The remainder of Section III describes how RfDs for PFOA, PFOS, PFNA and PFHxS were derived following evaluation of relevant studies and technical comments submitted to NHDES by April 12th, 2019, as well as scientific uncertainties specific to the RfDs.

Perfluorooctanoic acid or perfluorooctanoate (PFOA), CAS# 335-67-1

Principal study & consideration of health effects

For the derivation of a RfD and MCL for PFOA, NHDES recommends the critical health effect of increased relative liver weight (Loveless et al., 2006; NJDWQI 2017) as an indicator for the onset of hepatotoxicity. This is the same critical health effect previously selected in the initial MCL proposal (NHDES 2019), and based on review of the literature and technical comments received, NHDES remains confident in this recommendation.

Since the initial MCL proposal by NHDES at the start of January 2019, additional studies have been published related to associations between PFOA and human health impacts along with studies demonstrating toxicity in rodent models. Relative to the critical effect proposed by NHDES, there are three new studies that merit acknowledgment with regard to relative liver toxicity. This includes two studies from highly-exposed populations (Bassler et al., 2019; Nian et al., 2019) and evaluation of background exposure levels from the 2011-2014 NHANES dataset (Jain and Ducatman 2019). Bassler and colleagues (2019) reported associations between non-clinical biomarkers of hepatocyte apoptosis (cell death) as well as altered inflammatory disease of the liver with exposure to PFOA and other PFAS within a subset of subjects from the C8 Cohort (mean PFOA serum level 94.6 ng/mL). In the C8 Health Study of China (n = 1,605 participants, median PFOA serum level of 6.19 ng/mL), liver enzyme markers such as ALT and AST showed significant increases with natural log (ln)-unit changes of PFOA, other PFAS and their isomers (Nian et al., 2019). Analysis of the 2011-2014 NHANES data (n=2,883 subjects) detected consistent associations between PFAS, including PFOA, and increased ALT and GGT in obese individuals. It is noted that the cross-sectional design of certain studies and the lack of adjustments for false discovery following multiple comparisons underscore typical challenges of relying on epidemiological studies to demonstrate causal relationships, or their utility for determining the POD in RfD development. Qualitatively, these studies reinforce NHDES consideration of altered liver function and hypertrophy in rodents as a critical health effect for the basis of its PFOA RfD.

Studies published prior to 2019 were considered as a part of the initial PFAS MCL proposal put forward by NHDES (2019). This included evaluation of peer-reviewed evidence for:

- associated immunotoxicity as summarized by the National Toxicology Program (NTP 2016), ATSDR (2018b), DeWitt et al., (2012), Kirk et al., (2018) and Chang et al., (2016),
- developmental toxicity in animal models (Butenhoff et al., 2004; Lau et al., 2006; White et al., 2007; Wolf et al., 2007; Hu et al., 2010; Onishchenko et al., 2011; White et al., 2011; Albrecht et al., 2013; Cheng et al., 2013; Koustas et al., 2014; Quist et al., 2015ab; Koskela et al., 2016), associated fetal and neonatal growth impacts in humans (reviewed by Verner et al., 2015; Negri et al., 2017; Rappazzo et al., 2017; Liew et al., 2018 and ATSDR 2018b) and consideration of developmental outcomes evaluated in the U.S. EPA LHA for PFOA of 70 ng/L (EPA 2016a),
- associated human-health outcomes based on the C8 studies (Frisbee et al., 2009, 2010; Steenland et al., 2009, 2010ab, 2013; Stein et al. 2009, 2013; Lopez-Espinosa et al., 2011, 2012ab; Gallo et al., 2012; Savitz et al., 2012ab; Steenland and Woskie 2012; Barry et al., 2013; Darrow et al., 2013; Fletcher et al., 2013; Vieira et al., 2013; Watkins et al., 2013; Winquist et al., 2013; Darrow et al., 2016),

- and delayed mammary gland development in mice (White et al., 2007, 2009, 2011; Macon et al., 2011; Tucker et al., 2015).

In its initial proposal, NHDES agreed with the assessment made by the New Jersey Drinking Water Quality Institute (NJDWQI) relative to adverse effects on the liver and NHDES maintains this position. In their 2017 document, NJDWQI summarized evidence from studies in non-human primates, various strains of rodents, including PPARα knock-out mice, as well as the existing epidemiologic studies. This lead the NJDWQI to the conclusion that there was "consistency among non-occupational studies, as well as evidence of specificity, exposure-response, strength, and biological plausibility for PFOA and ALT. These findings provide evidence supporting a causal relationship between PFOA and ALT" (NJDWQI 2017). They also acknowledge the limited epidemiologic evidence, as of 2017, to definitively prove a causal relationship with PFOA and liver disease, and the available studies did not find an association. (NJDWQI 2017). While NHDES does not agree with the application of a full database uncertainty factor (NJDWQI 2018), the arguments made for consideration of hepatic effects for human health risk assessment were deemed appropriate given the existing information on PFOA.

The ATSDR 2018 draft toxicity profile for perfluoroalkyls recognized the likely associations between PFOA and hepatotoxicity (e.g., increased serum enzyme concentrations and effects on serum bilirubin) after consideration of similar epidemiological studies and the NJDWQI 2017 report (NJDWQI 2017; ATSDR 2018b). After additional review of this same document (ATSDR 2018b), NHDES agrees there is concern for the associations between exposure to PFOA and the following human health outcomes: increases in serum lipids (i.e., total and LDL cholesterol), disruption of thyroid hormone function and transport, decreased vaccine response, decreased fertility and reduced birth weight. The scientific evidence is less clear regarding other suggested human health associations and merit further investigation to establish whether these effects are truly linked to PFOA exposure. As this relates to the RfD derived by NHDES, it was determined that the animal study selected by ATSDR was not appropriate for RfD derivation following NHDES understanding of EPA methodology (EPA 2002) and was therefore not selected for use in the initial or final MCL proposal.

Regarding carcinogenicity, NHDES derived a PFOA MCL based on non-cancer endpoints. The U.S. EPA and International Agency for Research on Cancer (IARC) determined that the current evidence indicates that PFOA is a suggestive (EPA 2016) or possible (IARC 2016) carcinogen in humans. This is specific to suggestive evidence for increased risks of kidney and testicular cancer seen in rodents and mixed associations from human studies (Barry et al., 2013). Two other agencies, the USEPA (2016a) and NJDWQI (2017), have derived cancer values for PFOA using the same principal rodent study for PFOA carcinogenicity (Butenhoff et al. 2012). The U.S. EPA (2016a) and NJDWQI (2017) arrived at possible MCL values of 500 ng/L and 14 ng/L, respectively, for a one-in-a-million risk for testicular cancer. More recently, the California Office of Environmental Health Hazard Assessment (2019) has recommended a similar value of 14 ng/L for PFOA citing concern for liver damage and cancer. This discrepancy in cancer-based MCL estimates highlights the need for better information to inform cancer risk assessment for PFOA, and is expected to be an evolving area of research in years to come. Regardless of whichever is the more accurate assessment, the proposed MCL for PFOA is lower than the more conservative of these two estimates.

Determination of a point of departure

As previously proposed by NHDES (2019), the principal study and point of departure (POD) was the same study (Loveless et al., 2006) recommended and benchmark dose modeled by the NJDWQI (2017). The critical health effect was increased relative liver weight in male mice following a 14-d oral exposure to APFO (Loveless et al., 2006). There is consistent evidence for liver toxicity across wild-type and PPARα knock-out mice (Butenhoff et al., 2004; Loveless et al., 2008; Son et al., 2008; Cui et al., 2009; Elcombe et al., 2010; Yahia et al., 2010; Tan et al., 2013; Wang et al., 2015; Rebholz et al., 2016; Li et al., 2017), as well as persistent effect on liver size and structure following gestational exposure to similar dosing regimens (Quist et al., 2015). Rat studies have suggested that this effect is an adaptive response that will dissipate following cessation of the exposure to PFOA (Butenhoff et al., 2004; Hall et al., 2012). Beyond rodent models, cynomolgus monkeys display hepatic hypertrophy, increased serum triglycerides and decreased serum T_4 following chronic exposure (26 weeks) to APFO (Butenhoff et al., 2002). As it relates to the present human health risk assessment for an MCL, these effects are not entirely adaptive as animal studies suggest persistent changes in the liver following exposure during early life stages (Quist et al., 2015a). NHDES also maintains its previous position that whether the response is adaptive is not relevant to drinking water exposures as the general population should not require recovery periods from public water. Furthermore, unlike rodents that display relatively short half-lives for PFOA and other PFAS, once humans are exposed to increased levels of PFOA they will maintain elevated serum levels on a time scale of months to years. This means that brief external exposures become chronic internal doses, especially if the external dose is relatively high. The effects on liver function are considered a chronic health outcome based on the existing body of literature.

This POD is based on the benchmark dose modeling work conducted by the NJDWQI (2017) in their technical documents for their proposed RfD and MCL of 2.0 ng/kg-d and 14 ng/L, respectively, that identified a POD for PFOA of 4,351 ng/mL based on increased liver weight. NHDES did not arrive at the same RfD due to differences in the application of uncertainty factors. Differences in the final MCL are due to NH's use of the transgenerational exposure model for breastfeeding (Goeden et al., 2019).

Application of uncertainty factors

A total uncertainty factor of 100 was applied to the POD for PFOA based on:

Intraspecies variability (10) × Interspecies variability (3) × Database limitations (3) = 100

For the non-risk assessor, the units of 3 and 10 are for partial (half) and full log units. So, a full log unit of 10 equals 10^1, but a half log unit of $10^{½}$ or $10^{0.5}$ is equal to 3.162. As a convention of risk assessment using EPA methodology (EPA 2002), the value of 3.162 is presented as 3. Thus, 10 × 3 × 3 is rounded to 100 from 99.982.

The full factor of 10 for intraspecies variability was deemed appropriate to protect for the poorly characterized differences in toxico-dynamics (× 3) and -kinetics (× 3) within the human population. As NHDES applied a DAF to convert the rodent serum concentration to an oral human dose, only a partial uncertainty factor (× 3) was applied for interspecies variability. As the NJDWQI (2017) derived a benchmark dose, there was no need for any additional uncertainty factors to account for lowest

observed adverse effect level (LOAEL) to no observed adverse effect level (NOAEL) conversion. As the critical effect of hepatic hypertrophy is considered the onset of the adverse effect in a sensitive model species, no additional uncertainty factor was applied to account for acute-to-chronic duration of exposure.

Although NHDES agrees with the NJDWQI selection of a critical health effect and derivation of the POD for PFOA (NJDWQI 2017), NHDES concluded there is insufficient evidence supporting the application of the more conservative full database uncertainty factor (× 10). In technical comments submitted on the initially proposed MCLs, this decision was the subject of multiple critiques. On one hand, some have argued the use of a partial uncertainty factor was under-protective as the NJDWQI applied a full factor (× 10) due to concerns for observations of delayed mammary gland development in mice exposed to PFOA during perinatal development (NJDWQI 2017, and references therein). NHDES notes that the USEPA LHA (2016a) and CDC's ATSDR draft report (2018b) did not apply any database uncertainty factor with respect to the mammary gland development studies in rodents given the lack of clarity towards human health relevance (Table 3). Similar to New Hampshire, two other state agencies, Minnesota (MDH 2018) and New York (presentation, October, 2018), derived RfDs for PFOA affording only a partial uncertainty factor for this and other adverse health impacts observed in rodent and epidemiological studies. It should be noted that both of these other agencies did not use the same POD as NJDWQI or NHDES, where Minnesota utilized a higher POD and New York utilized a lower POD compared to the benchmark dose (BMD) value from Loveless et al., (2006). Thus, NHDES believes that the application of a partial database uncertainty factor (× 3) is appropriately protective without being overly conservative given the critical health effect selected and the existing toxicological and epidemiological database.

Estimation of a human equivalent oral dose

The POD represents an internal animal serum level associated with the adverse health outcome of concern. Dividing the POD by the total uncertainty factor yields a protective target serum level equivalent for the human population. *This is not a clinical or diagnostic value, nor should it be interpreted as such*.

$$\text{Target serum level for PFOA} = \frac{4{,}351 \text{ ng/mL}}{100} = 43.5 \text{ ng/mL}$$

To estimate how this internal blood level corresponds to an external oral dose of the specified compound, a dosimetric adjustment factor is applied by multiplication to identify a dose in ng of specified PFAS, per kg of individual body weight, per day (ng/kg-d). This step accounts for the highly-bioaccumulative nature and unique half-life estimates of each compound, and is consistent with prior risk assessment methods for derivation of RfDs for PFAS (USEPA 2016ab; NJDWQI 2017, 2018a; ATSDR 2018b; MDH 2018, 2019ab). The human equivalent oral dose is estimated by the following equations:

$$\text{Reference dose (RfD)} = \frac{\text{Point of departure (POD)}}{\text{Total uncertainty factors (UF)}} \times \text{Dosimetric adjustment factor (DAF)}$$

Where the DAF is equal to,

$$DAF = V_d \times \left(\frac{Ln(2)}{t_{1/2}}\right)$$

$$DAF = 170\ mL/kg \times \left(\frac{Ln(2)}{840\ days}\right) = 1.40\times10^{-1}\ mL/kg\text{-}d$$

Consistent with the initial PFOA MCL proposal (NHDES 2019), the volume of distribution (V_d) for PFOA was 170 mL/kg (Thompson et al., 2010; EPA, 2016a). For its revised and final proposal, NHDES selected the serum half-life of 2.3 years for PFOA (Bartell et al., 2010). NHDES acknowledges that the half-life of 2.3 years is slightly less conservative than the initially proposed value for RfD derivation of 2.7 years (Li et al. 2018; NHDES 2019). This change was due, in part, to the consideration of this half-life being more appropriate given the significantly higher exposure specific to PFOA described in Bartell et al. (2010) and the larger sample size than that in Li et al. (2018).

Thus, using this chemical-specific DAF and the aforementioned point of departure and uncertainty factors, NHDES derived an oral reference dose for PFOA of 6.1 ng/kg-d.

$$\text{Reference dose (RfD)} = \frac{4{,}351\ ng/mL}{100} \times 1.40\times10^{-1}\ mL/kg\text{-}d = 6.1\ ng/kg\text{-}d$$

Perfluorooctane sulfonic acid or perfluorooctane sulfonate (PFOS), CAS# 1763-23-1

Principal study & consideration of health effects

For the derivation of a RfD for PFOS, NHDES recommends the critical health effect of suppressed immunoglobulin M (IgM) production in male mice as proposed by the Minnesota Department of Health (Dong et al., 2011; MDH, 2019a). While NHDES previously proposed a RfD based on developmental toxicity, the review of existing and emerging evidence and technical comments suggest that the use of this immunotoxic endpoint represents a more appropriately cautious approach for the risk assessment of PFOS.

Since the initial MCL proposal by NHDES at the start of January 2019, additional studies have been published related to associations between PFOS and human health impacts along with studies demonstrating toxicity in rodent models. In the same studies that found associations between PFOA and serological markers of liver function (Nian et al., 2019; Jain and Ducatman, 2019; Bassler et al., 2019), PFOS was also associated with liver dysfunction and markers of hepatic inflammatory responses. Relative to the critical health effect selected by NHDES, one additional study on immunosuppression in humans was published since January 2019. In a prospective study of 3-month old infants from China (n = 201 participants), cord blood levels of branched isomers of PFOS were associated with reduced concentrations of antibodies towards enterovirus 71 (a causative viral agent of hand-foot-and-mouth disease; Zeng et al., 2019). Aside from hepatic and immune effects, additional studies have suggested associations between prenatal PFOS levels and early onset of puberty in girls from the Danish Birth Cohort (Ernst et al., 2019) and an estrogen-mediated relationship between cord blood levels of PFOS and birth weight (Wang et al., 2019). As with many epidemiological studies on PFAS, many of these recent studies possessed various combinations of limitations including a lack of analysis for other environmental contaminants, limited sample size and lack of analysis for the influence of breastfeeding. However, they collectively demonstrate that there is a growing body of evidence for adverse health impacts associated with PFOS.

Studies published prior to 2019 were considered as a part of the initial PFAS MCL proposal put forward by NHDES (2019). This included evaluation of peer-reviewed evidence for:

- immunotoxicity as summarized by the National Toxicology Program (NTP 2016), ATSDR (2018b) DeWitt et al., (2012) and Chang et al., (2016),
- developmental toxicity in animal models (Lau et al., 2003; Thibodeaux et al., 2003; Luebker et al., 2005ab; Yahia et al., 2008; Butenhoff et al., 2009; Onishchenko et al., 2011; Rogers et al., 2014; Wan et al., 2014), fetal and neonatal growth impacts in humans (reviewed by Verner et al., 2015; Negri et al., 2017; Rappazzo et al., 2017; Liew et al., 2018 and ATSDR 2018b) and consideration of delayed development in the U.S. EPA LHA for PFOS of 70 ng/L (EPA 2016b),
- neurobehavioral and thyroid hormone-associated effects (as reviewed by ATSDR 2018b).

NHDES acknowledges that the current understanding of the immunotoxic effects of PFOS, other PFAS and their interactions is an evolving area of research. As described by DeWitt et al. (2019), the interpretation of immunosuppression is important to consider when evaluating the relevance of associated outcomes from human studies, as well as measured responses from rodents. The current body of literature is not mature enough to clearly evaluate clinical relevance to humans, or lack thereof

(Chang et al., 2016); however, the NTP (2016) concluded that PFOS is "presumed to be an immune hazard to humans" based on animal and human data available at that time. Mouse studies indicate that PFOS impairs the T cell-dependent antibody response at low doses following sub-chronic exposure durations (Dong et al., 2009, 2011; reviewed by DeWitt et al., 2012, 2019), and was selected as the basis for a PFOS RfD by several agencies including NJDWQI (NJDWQI 2018; further detailed by Pachkowski et al. 2019), NYDOH (2018) and proposed by MDH (2019a). Although the ATSDR MRL for PFOS was based on developmental delays (Luebker et al., 2005ab), they applied an additional uncertainty factor of 10 due to the evidence for immunotoxicity (ATSDR, 2018b). Collectively, this indicates that the lower dose range at which the immunotoxic effects occur in rodents is recognized as an appropriately protective range for selection of a POD. There is a critical need for replication and use of larger study populations for understanding the immunomodulatory associations reported for PFOS and other PFAS.

NHDES derived a PFOS MCL based on non-cancer endpoints due to a lack of adequate carcinogenicity studies. IARC has not classified the carcinogenicity of PFOS at this time. The U.S. EPA determined that PFOS was a suggestive carcinogen (EPA, 2016b). This is specific to suggestive evidence for increased incidence of liver and thyroid adenomas in rats following chronic exposure. The recommendation of using non-cancer endpoints over cancer endpoints is not unique to NHDES, as other agencies have concluded that non-cancer health endpoints are adequately protective (MDH 2018; Michigan PFAS Science Advisory Panel 2018). Should additional information become available that is adequate for derivation of a cancer slope factor (CSF) for PFOS, NHDES will consider this in the framework of the MCL process.

Determination of point of departure

Following review of the technical documents deriving RfDs for PFOS based on immunosuppression in mice (NJDWQI, 2018; ATSDR 2018b; Pachkowski et al., 2019; MDH, 2019), NHDES agreed with the RfD derivation recently proposed by the Minnesota Department of Health (MDH 2019). This POD is based on serum concentrations of PFOS at the no observable adverse effect level (NOAEL) for suppressed IgM production in male mice following 60-d oral exposure (Dong et al. 2011). As summarized by MDH (2019), the critical effect reported in Dong et al. (2011) was suppressed IgM production with a NOAEL of 2,620 ng/mL (oral dose, 0.0167 mg/kg-d) and a LOAEL of 10,750 ng/mL (oral dose, 0.083 mg/kg-d). A prior study by Dong et al. (2009) reported a NOAEL of 674 ng/mL (oral dose, 0.008 mg/kg-d) for reduced plaque forming cell response to sheep red blood cells, and a similar oral LOAEL as Dong et al. (2011). However, the early work by Dong et al. (2009) did not include the intermediate dose of 0.0167 mg/kg-d that was identified as a NOAEL in their later work (Dong et al. 2011). This is further complicated as the specific effect was not replicated in both studies where plaque forming cell response was only measured in Dong et al. (2009) and IgM concentrations in the later Dong et al. (2011). As both of these metrics describe different aspects of the same immune process they do support the consideration of immunosuppression at these low doses as a POD. There remains the issue of discordance in dosing. While benchmark dose modeling of these endpoints using the original data might prove valuable to demonstrating these different metrics support a similar POD, the original data was not available for modeling and the reported data has been described as unamenable to benchmark dose modeling (NJDWQI 2018). As a result, NHDES agreed with the use of the NOAEL (2,620 ng/mL) for IgM suppression (Dong et al., 2011) instead of the lower NOAEL of 674 ng/mL (Dong et al., 2009) as a POD.

Application of uncertainty factors

A total uncertainty factor of 100 was applied to the POD for PFOS based on:

Intraspecies variability (10) × Interspecies variability (3) × Database limitations (3) = 100

For the non-risk assessor, the units of 3 and 10 are for partial (half) and full log units. So, a full log unit of 10 equals 10^1, but a half log unit of $10^{½}$ or $10^{0.5}$ is equal to 3.162. As a convention of risk assessment using EPA methodology (EPA 2002), the value of 3.162 is presented as 3. Thus, 10 × 3 × 3 is rounded to 100 from 99.982.

The full factor of 10 for intraspecies variability was deemed appropriate to protect for the poorly characterized differences in toxico-dynamics (× 3) and -kinetics (× 3) within the human population. As NHDES applied a DAF to convert the rodent serum concentration to an oral human dose, only a partial uncertainty factor (× 3) was applied for interspecies variability. The POD was based on the NOAEL described in Dong et al. (2011); thus, there was no need for additional uncertainty factors to account for LOAEL to NOAEL conversion. Dong et al. (2011) conducted a 60-day exposure so no additional uncertainty factor was applied for acute-to-chronic duration of exposure. As described by MDH (2019), an additional partial (× 3) database uncertainty factor was applied due to concerns for reports of thyroid disruption (decreased T_4) in neonatal animals and the implications of these observations in terms of neurodevelopment that has not yet been adequately studied. NHDES agreed with this consideration given the suggestive evidence for the human relevance of altered T_4 levels (reviewed by Ballesteros et al., 2017 and ATSDR, 2018b) and their potential implications for impaired neurodevelopment in humans (Grandjean and Landrigan, 2014).

Estimation of a human equivalent oral dose

The POD represents an internal animal serum level associated with the adverse health outcome of concern. Dividing the POD by the total uncertainty factor yields a protective target serum level equivalent for the human population. *This is not a clinical or diagnostic value, nor should it be interpreted as such*.

$$\text{Target serum level for PFOS} = \frac{2{,}360\ \text{ng/mL}}{100} = 23.6\ \text{ng/mL}$$

To estimate how this internal blood level corresponds to an external oral dose of the specified compound, a dosimetric adjustment factor is applied by multiplication to identify a dose in ng of specific PFAS per kg of individual body weight per day (ng/kg-d). This step accounts for the highly-bioaccumulative nature and unique half-life estimates of each compound, and is consistent with prior risk assessment methods for derivation of RfDs for PFAS (EPA, 2016ab; NJDWQI, 2017, 2018a; ATSDR, 2018b; MDH, 2018, 2019ab). The human equivalent oral dose is estimated by the following equations:

$$\text{Reference dose (RfD)} = \frac{\text{Point of departure (POD)}}{\text{Total uncertainty factors (UF)}} \times \text{Dosimetric adjustment factor (DAF)}$$

Where the DAF is equal to,

$$DAF = V_d \times \left(\frac{Ln(2)}{t_{1/2}}\right)$$

$$DAF = 230\ mL/kg \times \left(\frac{Ln(2)}{1{,}241\ days}\right) = 1.28\times10^{-1}\ mL/kg\text{-}d$$

Consistent with the initial PFOS MCL proposal (NHDES 2019), the V_d for PFOS was 230 mL/kg (Thompson et al., 2010). In its revised and final proposal, NHDES maintains its use of a 3.4-year half-life estimate based on the average across men and women, described in Li et al. (2018; NHDES 2019). NHDES considered the longer half-life values reported for retired fluorochemical workers (Olsen et al. 2007), and deemed these to be inappropriately conservative given the use of the Minnesota transgenerational model for exposure assessment which emphasizes early-life and breastfeeding exposures.

Thus, using this chemical-specific DAF and the aforementioned point of departure and uncertainty factors, NHDES derived an oral reference dose for PFOS of 3.0 ng/kg-d.

$$\text{Reference dose (RfD)} = \frac{2{,}360\ ng/mL}{100} \times 1.28\times10^{-1}\ mL/kg\text{-}d = 3.0\ ng/kg\text{-}d$$

Perfluorononanoic acid or perfluorononanoate (PFNA), CAS# 375-95-1

Principal study & consideration of health effects

For the derivation of a RfD and MCL for PFNA, NHDES recommends the critical health effect of increased relative liver weight in pregnant mice (Das et al., 2015; NJDWQI, 2018) as an indicator for the onset of hepatotoxicity. This is the same critical health effect previously selected in the initial MCL proposal (NHDES, 2019), and based on additional review of the literature NHDES remains confident in this decision.

Since the initial MCL proposal by NHDES at the start of January 2019, additional studies have been published related to associations between PFNA and associated human health impacts along with studies demonstrating toxicity in rodent models. In the same studies that found associations between PFOA and serological markers of liver function (Nian et al., 2019; Jain and Ducatman, 2019; Bassler et al., 2019), PFNA was also associated with liver dysfunction and markers of hepatic inflammatory responses. As discussed later, this co-association between multiple PFAS and the same health outcomes is acknowledged as a present challenge of epidemiological research. The same study of the Danish Birth Cohort that associated PFOS with an early onset of puberty in girls found that prenatal serum levels of PFNA were associated with delayed onset of puberty in boys (Ernst et al., 2019). Ernst and colleagues (2019) noted that these associations merit caution in their interpretation and require replication due to their novelty. Unlike PFOA and PFOS, PFNA has been the subject of relatively less research and its lower background serum concentrations compared to PFOA and PFOS present a challenge to identifying its effects in human populations.

Studies published prior to 2019 were considered as a part of the initial PFAS MCL proposal put forward by NHDES (2019). At the time, two major documents reviewed the toxicity of PFNA in humans and rodents (NJDWQI, 2018; ATSDR, 2018b). As noted in both documents, relatively little research has been conducted on PFNA despite its historical use and presence in a variety of environmental media. The NJDWQI concluded there was limited evidence associating PFNA with changes in serum ALT as a biomarker of hepatotoxicity (NJDWQI, 2018), whereas the ATSDR determined these inconsistencies in epidemiological data did not merit inclusion of hepatotoxicity as an associated health outcome for PFNA (ATSDR, 2018b). In its initial proposal, NHDES agreed with the assessment made by the NJDWQI relative to adverse effects on the liver and NHDES maintains this position. Given the limited amount of epidemiological data currently available for PFNA and its similarity in chemical structure to PFOA and biological activities in animal models, NHDES determined that the associated hepatotoxic effects were more relevant and sensitive for human health risk assessment than the developmental and endocrine effects reported in animal studies. While NHDES does not agree with the application of the database uncertainty factor or animal-to-human dose extrapolation, the arguments made for consideration of hepatotoxicity by NJDWQI (2018) were deemed appropriate given the existing information.

To date, the carcinogenicity of PFNA has not been reported in a rodent model. The human carcinogenicity of PFNA has not been classified by the U.S. EPA, IARC or CDC (ATSDR). Therefore, NHDES did not conduct a cancer-based risk assessment for PFNA. Should additional information become available that is adequate for consideration of a cancer slope factor (CSF) for PFNA, NHDES recommends consideration as to whether its development and application of such values would be more protective than the proposed MCL.

Determination of a point of departure

As previously proposed by NHDES (2019), the principal study and point of departure (POD) was the same study (Das et al., 2015) recommended and benchmark dose modeled by the NJDWQI (2018). The critical health effect was increased relative liver weight in pregnant mice following a 17-d (duration of gestation) oral exposure to PFNA (Das et al., 2015). The internal LOAEL for these mice was 12,400 ng/mL which corresponded to an oral dose of 1.0 mg/kg-d (Das et al., 2015). While no significant mortality was observed at this dose, higher oral doses (>5.0 mg/kg-d) were associated with neonatal mortality in mice. Wolf et al. (2010) demonstrated the profound effects of PFNA on mouse pups were due to PPARα activation which raises uncertainty about the qualitative and quantitative relevance of this outcome to human health. Additional studies demonstrate that rodent models display hepatotoxic responses towards PFNA (Wolf et al., 2010; Wang et al., 2015), with evidence of PPARα-independent mechanisms (Rosen et al., 2017).

This POD is based on the benchmark dose modeling work conducted by the NJDWQI (2018) in their technical documents for their proposed MCL of 13 ng/L. It should be noted that NJDWQI did not derive a RfD as a part of the MCL development, as a ratio method was used instead of a DAF with water ingestion rate to convert the target serum level to a corresponding water concentration. NHDES did not arrive at the same MCL because NHDES opted to derive a RfD consistent with the other PFAS evaluated, as well as use of the transgenerational exposure model for breastfeeding (Goeden et al., 2019; MIDHHS, 2019).

Application of uncertainty factors

A total uncertainty factor of 100 was applied to the POD for PFNA based on:

Intraspecies variability (10) × Interspecies variability (3) × Database limitations (3) = 100

For the non-risk assessor, the units of 3 and 10 are for partial (half) and full log units. So, a full log unit of 10 equals 10^{1}, but a half log unit of $10^{½}$ or $10^{0.5}$ is equal to 3.162. As a convention of risk assessment using EPA methodology (EPA 2002), the value of 3.162 is presented as 3. Thus, 10 × 3 × 3 is rounded to 100 from 99.982.

The full factor of 10 for intraspecies variability was deemed appropriate to protect for the poorly characterized differences in toxico-dynamics (× 3) and -kinetics (× 3) within the human population. As NHDES applied a DAF to convert the rodent serum concentration to an oral human dose, only a partial uncertainty factor (× 3) was applied for interspecies variability. As the NJDWQI (2018) derived a benchmark dose, there was no need for any additional uncertainty factors to account for LOAEL to NOAEL conversion. As with PFOA, the critical effect of hepatic hypertrophy is considered the onset of the adverse effect in a sensitive model species. Consistent with PFOA, no additional uncertainty factor was applied to account for acute-to-chronic duration of exposure. The NJDWQI applied a full LOAEL to NOAEL uncertainty factor (× 10) to account for differences between the 17-d exposure in Das et al. (2015) and longer exposures resulting in reported adverse effects (summarized in NJDWQI, 2018). As increased liver weight in mice is already considered to be a highly-sensitive critical effect in response to PFAS, NHDES determined this was overly conservative given similar uncertainty factor considerations for the similar perfluorinated carboxylic acid, PFOA.

In its original proposal, NHDES applied a full database uncertainty factor (× 10) to account for the limited existing literature on PFNA (× 3), as well as the absence of a serum-derived human half-life estimate (× 3; NHDES 2019). As a part of its revision to the proposed RfDs and subsequent MCLs, NHDES utilized the more conservative half-life of PFNA derived for men and older women. Given the application of this more conservative half-life estimate, NHDES removed the associated partial uncertainty factor for PFNA. NHDES retained the partial uncertainty factor of × 3 to account for a lack of multigenerational rodent studies using PFNA, as well as concern for potential immunotoxic impacts seen with other PFAS (NTP 2016; DeWitt et al., 2012, 2019).

Estimation of a human equivalent oral dose

The POD represents an internal animal serum level associated with the adverse health outcome of concern. Dividing the POD by the total uncertainty factor yields a protective target serum level equivalent for the human population. *This is not a clinical or diagnostic value, nor should it be interpreted as such*.

$$\text{Target serum level for PFNA} = \frac{4{,}900\ \text{ng/mL}}{100} = 49.0\ \text{ng/mL}$$

To estimate how this internal blood level corresponds to an external oral dose of the specified compound, a dosimetric adjustment factor is applied by multiplication to identify a dose in ng of specific PFAS per kg of individual body weight per day (ng/kg-d). This step accounts for the highly-bioaccumulative nature and unique half-life estimates of each compound, and is consistent with prior risk assessment methods for derivation of RfDs for PFAS (USEPA 2016ab; NJDWQI 2017, 2018a; ATSDR 2018b; MDH 2019ab). The human equivalent oral dose is estimated by the following equations:

$$\text{Reference dose (RfD)} = \frac{\text{Point of departure (POD)}}{\text{Total uncertainty factors (UF)}} \times \text{Dosimetric adjustment factor (DAF)}$$

Where the DAF is equal to,

$$\text{DAF} = V_d \times \left(\frac{\text{Ln}(2)}{t_{1/2}}\right)$$

$$\text{DAF} = 200\ \text{mL/kg} \times \left(\frac{\text{Ln}(2)}{1{,}570\ \text{days}}\right) = 8.83 \times 10^{-2}\ \text{mL/kg-d}$$

Consistent with the initial PFNA MCL proposal (NHDES 2019), the V_d for PFNA was 200 mL/kg based on similar assumptions made by ATSDR (ATSDR 2018b). In this revised proposal, NHDES adjusted the half-life value from 2.5 to 4.3 years based on urinary half-lives estimated for men and older women, groups that tend to eliminate PFAS slower than younger and reproductive age women (Zhang et al., 2013; NHDES, 2019). As previously discussed in its initial proposal (NHDES, 2019), NHDES would prefer to have more reliable serum half-life estimates for PFNA instead of the urinary-derived estimates reported by Zhang and colleagues (2013). However, since the submission of the initial proposal no additional studies have been published that report a serum-based estimate for the half-life of PFNA in humans. Should additional peer-reviewed studies emerge that provide more rigorous estimates of these values, NHDES recommends consideration as to whether such data would represent and merit a significant change for the PFNA RfD.

Thus, using this chemical-specific DAF and the aforementioned point of departure and uncertainty factors, NHDES derived an oral reference dose for PFNA of 4.3 ng/kg-d.

$$\text{Reference dose (RfD)} = \frac{4{,}900 \text{ ng/mL}}{100} \times 8.83\times10^{-2} \text{ mL/kg-d} = 4.3 \text{ ng/kg-d}$$

Perfluorohexane sulfonic acid or perfluorohexane sulfonate (PFHxS), CAS# 355-46-4

Principal study & consideration of health effects

For the derivation of a RfD and MCL for PFHxS, NHDES recommends the critical health effect of impaired female reproduction as determined by reduced litter size initially reported in Chang et al. (2018). This RfD derivation is currently under peer-review with a scientific journal (Ali et al. *in review*). This is the same critical health effect previously proposed in the initial MCL proposal (NHDES 2019), albeit the present value is adjusted for benchmark dose modeling and selection of endpoint specific factors for dosimetric adjustment. NHDES developed the revised RfD in collaboration with external collaborators, Dr.'s Leah Stuchal and Stephen Roberts at the University of Florida, and awaits external peer-review on the soundness of its derivation. Should peer-review recommend revision and adjustment of the proposed RfD, NHDES will review the current MCL to determine if adjustments are required to be adequately protective of human health.

Since its initial proposal (NHDES, 2019), there has been a limited amount of new information generated relative to PFHxS. The Minnesota Department of Health proposed a RfD for PFHxS of 9.7 ng/kg-d based on reduced free T_4 in exposed rats using unpublished data from the NTP. At the time of writing this recommendation, the ATSDR has not released a revision to their 2018 draft MRL of 20 ng/kg-d based upon thyroid follicular cell damage in rats (ATSDR, 2018b). PFHxS showed similar associations with serological markers of liver function and inflammation as reported for PFOA, PFOS and PFNA (Nian et al., 2019; Jain and Ducatman, 2019; Bassler et al., 2019). Despite its legacy of widespread environmental occurrence associated primarily with AFFF use and growing regulatory interests, relatively little new toxicological information has emerged for PFHxS as of June 2019.

Studies published prior to 2019 were considered as a part of the initial PFAS MCL proposal put forward by NHDES (2019). This included re-evaluation of peer-reviewed evidence considered by ATSDR (2018b) including:

- thyroid toxicity including altered thyroid histology and reduced T_4 levels in rodent models (Butenhoff et al., 2008; Chang et al., 2018; Ramhøj et al., 2018), as well as epidemiology studies for altered T_4 levels (Ballesteros et al., 2017),
- immunomodulation in humans (Grandjean et al., 2012; Dong et al., 2013; Humblet et al., 2014; Okada et al., 2014; Buser and Scinicariello 2016; Stein et al., 2016; Zhu et al., 2016)
- reproductive and developmental toxicity in rodents (Butenhoff et al., 2008; Viberg et al., 2013; Chang et al., 2018; Ramhøj et al., 2018)
- hepatotoxicity or changes in lipid metabolism in rodents (Butenhoff et al., 2008; Bijland et al., 2011; Rosen et al., 2017; Chang et al., 2018; Ramhøj et al., 2018) and humans (Nelson et al., 2010; Starling et al., 2014; Mattsson et al. 2015).
- and human carcinogenicity (Hardell et al., 2010; Bonefel et al., 2014; Hurley et al., 2018).

To date, the carcinogenicity of PFHxS has not been reported in a rodent model. The human carcinogenicity of PFHxS has not been classified by the U.S. EPA, IARC or CDC (ATSDR). Therefore, NHDES did not conduct a cancer-based risk assessment for PFHxS. Should additional information become available that is adequate for consideration of a CSF for PFHxS, NHDES recommends consideration as to whether its development and application would be more protective than the proposed MCL.

Determination of a point of departure

As described in its initial MCL proposal (NHDES 2019), the principal study and point of departure (POD) was the same study (Chang et al., 2018) that has been adjusted primarily by use of benchmark dose modeling (Ali et al., *in review*). The critical health effect was reduced litter size in mice following a 14-d, prior to pregnancy, oral exposure to PFHxS (Chang et al., 2018). As mentioned above, the details and methodology for derivation of the POD for PFHxS are currently under review in Ali et al (*in review*). Benchmark dose (BMD) modeling was performed using Benchmark Dose Software (BMDS) (Version 3.1; USEPA, 2019). The critical effect endpoint was a change in the mean live litter size for adult CD-1 female mice, and due to the unavailability of litter-specific data was modeled based on PFHxS serum concentrations on study day 14 (reported in Chang et al., 2018). This resulted in a benchmark dose of 41,200 ng/mL and a 95% lower confidence limit on the benchmark dose (BMDL) of 13,900 ng/mL. NHDES determined that this is an appropriately cautious endpoint given the limited number of animal studies (reviewed in NHDES, 2019), considerably longer half-lives of PFHxS in humans when compared to other PFAS (Olsen et al., 2007; Zhang et al., 2013; Worley et al., 2017; Li et al., 2018), environmental occurrence and exposures (Daly et al., 2018), as well as suggestive associations of reproductive impacts in humans (Vélez et al., 2015; Zhou et al., 2017; Zhang et al., 2018).

Application of uncertainty factors

A total uncertainty factor of 300 was applied to the POD for PFHxS based on:

Intraspecies variability (10) × Interspecies variability (3) × Duration of exposure (3)
× Database limitations (3) = 300

For the non-risk assessor, the units of 3 and 10 are for partial (half) and full log units. So, a full log unit of 10 equals 10^1, but a half log unit of $10^{½}$ or $10^{0.5}$ is equal to 3.162. As a convention of risk assessment using EPA methodology (EPA 2002), the value of 3.162 is presented as 3. Thus, 10 × 3 × 3 × 3 is rounded to 300 from 316.14.

The full factor of 10 for intraspecies variability was deemed appropriate to protect for the poorly characterized differences in toxico-dynamics (× 3) and -kinetics (× 3) within the human population. As NHDES applied a DAF to convert the rodent serum concentration to an oral human dose, only a partial uncertainty factor (× 3) was applied for interspecies variability. As benchmark dose modeling was used to derive a POD, detailed in Ali et al. (*in review*), there was no need for any additional uncertainty factors to account for LOAEL to NOAEL conversion. After careful evaluation of technical comments and re-assessment of the literature and principal study, an additional but partial uncertainty factor (× 3) was applied to account for acute-to-chronic duration of exposure of female mice. In Chang et al. (2018), female mice received a less than chronic exposure (14 days) to PFHxS prior to the start of pregnancy. Because of the relatively limited number of studies on PFHxS and evidence for adverse impacts following longer exposure to similar compounds (i.e., PFOS), this was determined to be appropriate without being overly conservative (e.g., a full factor of × 10).

In its original proposal, NHDES applied a full database uncertainty factor (× 10) to account for the limited existing literature on PFHxS (× 3), as well as associations with thyroid hormone and transport interference (× 3; NHDES 2019). As a part of its revision to the proposed RfD and subsequent MCL,

NHDES determined the existing single-generation studies provide some basis for evaluating the reproductive and developmental toxicity of PFHxS. However, NHDES retained a partial uncertainty factor (× 3) to account for a lack of multigenerational rodent studies, as well as concern for potential immunotoxic impacts seen with other PFAS that have yet to be assessed (NTP 2016; DeWitt et al., 2019). The protracted human half-life of PFHxS relative to other PFAS underscores the need for additional research into biological impacts following chronic exposures.

Estimation of a human equivalent oral dose

The POD represents an internal animal serum level associated with the adverse health outcome of concern. Dividing the POD by the total uncertainty factor yields a protective target serum level equivalent for the human population. *This is not a clinical or diagnostic value, nor should it be interpreted as such*.

$$\text{Target serum level for PFHxS} = \frac{13{,}900\ \text{ng/mL}}{300} = 46.3\ \text{ng/mL}$$

To estimate how this internal blood level corresponds to an external oral dose of the specified compound, a dosimetric adjustment factor is applied by multiplication to identify a dose in ng of specific PFAS per kg of individual body weight per day (ng/kg-d). This step accounts for the highly-bioaccumulative nature and unique half-life estimates of each compound, and is consistent with prior risk assessment methods for derivation of RfDs for PFAS (USEPA 2016ab; NJDWQI 2017, 2018a; ATSDR 2018b; MDH 2019ab). The human equivalent oral dose is estimated by the following equations:

$$\text{Reference dose (RfD)} = \frac{\text{Point of departure (POD)}}{\text{Total uncertainty factors (UF)}} \times \text{Dosimetric adjustment factor (DAF)}$$

Where the DAF is equal to,

$$\text{DAF} = V_d \times \left(\frac{\text{Ln}(2)}{t_{1/2}}\right)$$

$$\text{DAF} = 213\ \text{mL/kg} \times \left(\frac{\text{Ln}(2)}{1{,}716\ \text{days}}\right) = 8.61\times10^{-2}\ \text{mL/kg-d}$$

In its revised MCL proposal for PFHxS, NHDES has changed both the V_d and half-life estimate for PFHxS to reflect the female-specific health impact utilized as the basis of the RfD. The V_d for PFHxS was reduced from 287 to 213 mL/kg which reflects a female-specific V_d value for PFHxS (Sundström et al., 2012). Sundström et al. (2012) reports the volume of distribution for cynomolgus monkeys, not humans, and no human V_d is currently available for PFHxS. Similar to ATSDR (ATSDR 2018b) and other agencies (MDH 2019b; MIDHHS 2019), NHDES used the non-human primate value as an estimate for the human volume of distribution. Similarly, NHDES adjusted the half-life value from 5.3 to the female-specific estimate of 4.7 years (average) based on a study of a community exposed to PFHxS through contaminated drinking water (Li et al. 2018; discussed in NHDES 2019). It is noted that use of this average half-life estimate for women is less conservative than longer average half-life estimates of 8.5 years (Olsen et al., 2007) or 7.4 years (Li et al., 2018) that rely on serum levels in men, or longer estimates of 7.7-35 years for women depending on age (Zhang et al., 2013). However, given the conservative nature and sex-specific effect selected for the POD of PFHxS, the use of a 4.7-year half-life in women was deemed appropriate without being overly-conservative.

Thus, using this chemical-specific DAF and the aforementioned point of departure and uncertainty factors, NHDES derived an oral reference dose for PFHxS of 4.0 ng/kg-d.

$$\text{Reference dose (RfD)} = \frac{13{,}900 \text{ ng/mL}}{300} \times 8.61\times10^{-2} \text{ mL/kg-d} = 4.0 \text{ ng/kg-d}$$

Summary of Recommended RfDs for PFOA, PFOS, PFNA and PFHxS

Recommended RfDs

NHDES recommends the following chronic oral RfDs for PFOA, PFOS, PFNA and PFHxS:

- PFOA, 6.1 ng/kg-d
- PFOS, 3.0 ng/kg-d
- PFNA, 4.3 ng/kg-d
- PFHxS, 4.0 ng/kg-d

These RfDs are for protection from the primary health effects of liver toxicity (PFOA and PFNA), immune suppression of antibody responses (PFOS) and reduced female fertility (PFHxS) based on evidence from animal studies. In addition to these primary health outcomes, these RfDs are expected to be reasonably protective for associated and secondary (less sensitive) health outcomes that occur at similar or higher serum concentrations in rodents. Secondary health effects for these and other PFAS include disruption of thyroid and sex hormone levels and their signaling, teratogenic effects, early-life growth delays, changes in cholesterol levels, neurobehavioral effects, renal toxicity and fertility in rodent models. NHDES believes its selection of PODs, uncertainty factors and DAFs for each RfD provides adequate protection of human health from appreciable risk of these primary and secondary health effects during a lifetime.

Table 2 presents the NHDES recommended RfDs or MRLs, along with their applied uncertainty factors those selected by other agencies that have evaluated these same PFAS. The application of uncertainty factors follows EPA guidance (EPA 2002), and is dependent on the principal study selected and consideration of other available studies. However, it is not uncommon for different risk assessors and toxicologists to arrive at different applications of uncertainty factors when considering where reasonable and health-protective conservatism is being applied in the risk assessment process.

Discussion of scientific uncertainties

While the human health effects of PFAS is a rapidly growing area of scientific research, the exact nature of their associated health effects in humans remains uncertain (ATSDR, 2018b; Michigan Panel, 2018). The cross-sectional nature of most epidemiological studies precludes proof of causality between measured PFAS serum concentrations and the reported associated health outcomes. This is especially problematic as the extraordinarily long half-lives of PFAS (years) make it difficult to disentangle the associated health effects in these studies from co-exposure to other environmental contaminants with relatively shorter half-lives (days to weeks). Additionally, there is a general lack of true control groups for comparison as various combinations of PFAS are detectable in the blood of virtually all populations from around the world. There is concern for the implications of reverse causation with certain health outcomes associated to PFAS. As an evolving area of scientific research, NHDES anticipates new findings will improve the understanding of PFAS-related health effects in humans.

Due to the limitations of epidemiological studies, RfDs were derived using animal data. There are inherent uncertainties associated with RfDs derived from animal studies (EPA 2002), specifically related

to considerations of human health relevance (e.g., biological plausibility) and translation of animal findings to human equivalent values (i.e., uncertainty factors and DAFs).

As a part of its initial proposal (NHDES, 2019), NHDES considered the contentious issue of peroxisome proliferator-activated receptor subtype α (PPARα) activation in rodents and its relevance to human health. The activation of PPARα is a contributing pathway for several of the reported toxic responses in rodent models evidenced by genetic knockout studies and gene expression profiling studies (reviewed by ATSDR 2018b and NHDES 2019). This is especially true for hepatotoxicity and changes in lipid metabolism in rodents following exposure to PFAS due to upregulation of rodent specific pathways leading to oxidative stress (Perkins et al., 2004; Loveless et al., 2006; Rosen et al., 2007, 2008, 2017; Das et al., 2017; reviewed by ATSDR, 2018b). *In vitro* testing demonstrates that PFAS show a stronger binding affinity for rodent PPARα when compared to human PPARα (Wolf et al., 2008). These and other studies reviewed by NHDES (2019) suggest qualitative and quantitative differences in toxicity between species for PPARα-dependent effects.

Such qualitative and quantitative differences raise concern for selection of critical health effects such as liver toxicity based on rodent studies (reviewed by Klaunig et al., 2012), and have been a major criticism of the half-lives derived by NHDES and other agencies for RfDs for PFOA, PFOS, PFNA and PFHxS. Based on existing toxicological information, NHDES contends that selected critical effects from animal studies are appropriate for the protection of human health. While the physiological roles of PPARs (i.e., PPARα, β and γ) in humans are less defined than those of the other nuclear receptors like the estrogen or androgen receptor, there is evidence that they are involved in lipid metabolism (Issemann and Green, 1990; Lee et al., 1995) and function of muscle, adipose and immune cells throughout the body (Tyagi et al., 2011). Independent of PPARα activation, there is evidence for other mechanisms for rodent toxicity (e.g. mitochondrial dysfunction) that are potentially relevant to humans and other organisms (Hagenaars et al., 2013; Cui et al., 2015; reviewed by Li et al., 2017; Li et al., 2018; NHDES, 2019). Furthermore, evidence from non-human primates further suggest that effects on the liver, cholesterol levels, thyroid hormones and the immune system are relevant to humans and not isolated to rodent studies (Griffith and Long 1980; Thomford 2001; Butenhoff et al., 2002; Seacat et al., 2002). Taken collectively, this supports the NHDES risk assessment and derivation of RfDs using the selected critical health effects.

With respect to uncertainty factors, NHDES received multiple comments regarding its application of uncertainty factors in the initially proposed MCLs (NHDES, 2019). Table 2 presents the uncertainty factors used by other state or federal agencies for the derivation of RfDs for PFOA, PFOS, PFNA or PFHxS, and demonstrates that NHDES's selections are within the norms of the professional practice. As previously explained for each compound, NHDES considered available information from human and animal studies to arrive at the total uncertainty factors applied for each RfD. Difference in principal study selection and consideration of available data results in differences in the selection and application of total uncertainty factors (EPA 2002). Given the selection of principal studies and considerations of exposure assumptions described in Section IV, NHDES remains confident that its application of uncertainty factors is appropriate without being overly conservative.

Table 2. Interagency Differences in Uncertainty Factors. Summary of uncertainty factor allocations, RfDs and MRLs by government risk assessment groups.

Specific Uncertainty Factors	ATSDR[a] (MRLs)	US EPA[b,c] (RfD)	TX CEQ[d] (RfD)	MN DOH[e-g] (RfD)	NJ DWQI[h-j] (RfD)	NH DES (RfD)	NY DOH[k] (RfD)
PFOA							
Principal Study	Koskela et al. 2016	Lau et al. 2006	Macon et al. 2011	Lau et al. 2006	Loveless et al. 2006	Loveless et al. 2006	Macon et al. 2011
Human Variability	10	10	10	10	10	10	10
Interspecies Differences	3	3	1	3	3	3	3
Duration of Exposure	1	1	1	1	1	1	1
LOAEL to NOAEL	10	10	30	1	1	1	1
Database Insufficiency	1	1	1	3	10	3	3
Total Uncertainty Factor	300	300	300	100	300	100	100
RfD (ng/kg-d)	3.0	20.0	12.0	18.0	2.0	6.1	1.5
PFOS							
Principal Study	Luebker et al. 2005	Luebker et al. 2005	Zeng et al. 2011	Dong et al. 2011	Dong et al. 2009	Dong et al. 2011	Dong et al. 2009
Human Variability	10	10	10	10	10	10	10
Interspecies Differences	3	3	1	3	3	3	3
Duration of Exposure	1	1	1	1	1	1	1
LOAEL to NOAEL	1	1	10	1	1	1	1
Database Insufficiency	10	10	1	3	1	3	1
Total Uncertainty Factor	300	300	100	100	30	100	30
RfD (ng/kg-d)	2.0	20.0	23.0	3.0	1.8	3.0	1.8
PFNA							
Principal Study	Das et al. 2015	n.a.	Fang et al. 2010	n.a.	Das et al. 2015	Das et al. 2015	n.a.
Human Variability	10	-	10	-	10	10	-
Interspecies Differences	3	-	1	-	3	3	-
Duration of Exposure	1	-	10	-	10	1	-
LOAEL to NOAEL	1	-	1	-	1	1	-
Database Insufficiency	10	-	10	-	3	3	-
Total Uncertainty Factor	300	-	1,000	-	1,000	100	-
RfD (ng/kg-d)	3.0		12.0		0.73	4.3	
PFHxS							
Principal Study	Butenhoff et al. 2009	n.a.	Hoberman & York 2003	Unpublished NTP data	n.a.	Chang et al. 2018	n.a.
Human Variability	10	-	10	10	-	10	-
Interspecies Differences	3	-	1	3	-	3	-
Duration of Exposure	1	-	1	1	-	3	-
LOAEL to NOAEL	1	-	3	1	-	1	-
Database Insufficiency	10	-	10	10	-	3	-
Total Uncertainty Factor	300	-	300	300	-	300	-
RfD (ng/kg-d)	20.0		3.8	9.7		4.0	

n.a. indicates the specific compound was not assessed or reported on by the specific agency.

[a] ATSDR, 2018b. Draft Toxicological Profile for Perfluoroalkyls

[b] U.S. EPA, 2016a. Health Effects Support Document for Perfluorooctanic Acid (PFOA)

[c] U.S. EPA, 2016b. Health Effects Support Document for Perfluorooctane Sulfonate (PFOS)

[d] TX Commission on Environmental Quality (TXCEQ), 2016. Perfluoro Compounds (PFCs): available at: https://www.tceq.texas.gov/assets/public/implementation/tox/evaluations/pfcs.pdf

[e] Minnesota Department of Health (MDH), 2018. Toxicological Summary for: Perfluorooctanoate.

[f] Minnesota Department of Health (MDH), 2019a. Toxicological Summary for: Perfluorooctane sulfonate.

[g] Minnesota Department of Health (MDH), 2019b. Toxicological Summary for: Perfluorohexane sulfonate.

[h] New Jersey Drinking Water Quality Institute (NJDWQI), 2017. Appendix A: Health-Based Maximum Contaminant Level Support Document: Perfluorooctanoic Acid (PFOA)

[i] New Jersey Drinking Water Quality Institute (NJDWQI), 2018a. Appendix A: Health-Based Maximum Contaminant Level Support Document: Perfluorooctane Sulfonate (PFOS)

[j] New Jersey Drinking Water Quality Institute (NJDWQI), 2018b. Appendix A: Health-Based Maximum Contaminant Level Support Document: Perfluorononanoic Acid (PFNA)

[k] New York Department of Health (NYDOH), 2018 and personal communications. Presentation available at: https://www.health.ny.gov/environmental/water/drinking/dwqc/

Section IV. Drinking Water Exposure Assumptions, Modeling and Resulting MCLs

Using the reference dose (RfD) derived in Section III, the MCL considers the estimated daily intake of water from a specific source and how much drinking water contributes to the total exposure from all other sources of a specified contaminant. Specific methodologies for deriving health protective water criteria are detailed by the EPA (USEPA 1989, 2004, 2017, 2018). Although NHDES chose a different approach, the conventional method for deriving drinking water values utilizes the following equation:

$$\text{Maximum contaminant level (ng/L)} = \frac{\text{Reference dose (ng/kg-d)}}{\text{Daily water ingestion rate (L/kg-d)}} \times \text{Relative source contribution (unitless)}$$

For a simple example, a drinking water value for PFOA using the currently recommended RfD, 95th percentile ingestion rate of lactating women and a relative source contribution of 0.5 (meaning 50%) is shown below. This approach was used in the initially proposed MCL, but is not being applied following consideration of breastfeeding (Goeden et al., 2019).

$$\text{Example for PFOA (not an actual MCL recommendation by NHDES)} = \frac{6.1 \text{ ng/kg-d}}{0.055 \text{ L/kg-d}} \times 0.5 = 55 \text{ ng/L}$$

The daily water ingestion rate is a body-weight adjusted factor specific to certain age groups, to gender, and to lactation or pregnancy status. In its initial proposal, NHDES selected the water ingestion rate of the 95th percentile of lactating women, an estimated value of 0.055 L/kg-d (EPA, 2011; NHDES, 2019). While lower estimates are more reflective of the central tendencies of the general population, especially non-lactating women, they were deemed inadequately protective for the larger population. The values are selected from the Exposure Factors Handbook (EPA 2011), which was recently updated specifically for these ingestion rates (see Chapter 3 of EPA, 2019). These updated values were used by NHDES.

Instead of applying a fixed daily water ingestion rate that is assumed to be protective across a lifespan, NHDES applied the toxicokinetic model described by Goeden et al. (2019) to consider how changes in water ingestion at a given MCL are predicted to influence internal blood levels of each PFAS. This is due to the prolonged and elevated internal doses (i.e., serum levels) predicted across infancy and childhood resulting from PFAS in breastmilk. NHDES acknowledges that this is a departure from typical methodology for deriving such a standard, but the unique properties of PFAS (i.e., long half-lives) merit its application to be truly protective across all life stages for the chronic health impacts associated with these chemicals.

The relative source contribution (RSC) is an estimate of how much of the typical daily exposure will be allowed to come from drinking water. EPA recommends an RSC floor of 20% of the RfD and a ceiling of 80% of the RfD. The intention of an RSC ceiling of 80% is to ensure that total exposure from all sources does not exceed 100% of the RfD with a margin of safety for potential unknown or underestimated exposures. PFAS are present in a wide variety of environmental media (Moriwaki et al., 2003; Trudel et al., 2008; Haug 2011; Haug et al., 2011; Winkens et al., 2017, 2018) and consumer products (Haug 2011; Carpet and Textile Treatment - Washburn et al., 2005; Winkens et al. 2017; Cosmetics - Kang et al., 2016; Fast Food Packaging – Schaider et al., 2017), with an ever-growing number of potential sources identified (Boronow et al., 2019; Kim et al., 2019; Nakayama et al., 2019). Thus, for the typical person, it is unlikely that drinking water is responsible for 100% of their exposure. However, an exact profile for the proportions of exposure from various sources remains poorly characterized. The latter part of this section details how this was evaluated by NHDES to arrive at a RSC of 50% for PFOA, PFOS, PFNA and PFHxS.

Application of Goeden et al. (2019) for exposure modeling

As a part of the evaluation of published research and technical comments on the initially proposed MCLs (NHDES, 2019), NHDES has adopted the use of the transgenerational toxicokinetic model (detailed in Goeden et al., 2019), for the determination of appropriately protective health-based MCLs. This is a toxicokinetic model that predicts the serum concentration of PFAS due to drinking water exposure and consumption of breastmilk or formula across a lifespan starting at birth (Goeden et al., 2019). It does not predict an effect (health outcome) due to exposure from drinking water, only the blood concentration for an individual in a reasonable maximum exposure (RME) scenario. The tolerable blood concentration in the RME scenario, or threshold, is determined by the chemical-specific RfD and RSC. This Excel-based model is available upon request from the MN Department of Health.

After review of the model and studies on the placental transfer (Fei et al., 2007; Midasch et al., 2007; Monroy et al., 2008; Fromme et al., 2010; Beesoon et al., 2011; Kim et al., 2011; Liu et al., 2011; Needham et al., 2011; Lee et al., 2013; Porpora et al., 2013; Zhang et al., 2013; Kato et al., 2014; Cariou et al., 2015; Manzano-Salgado et al., 2015; Fisher et al., 2016; Yang et al., 2016; Chen et al., 2017; Mamsen et al., 2019) and breastmilk transfer (Karrman et al., 2007; Haug et al., 2011; Kim et al., 2011; Liu et al., 2011; Cariou et al., 2015; Gyllenhammer et al., 2018) of PFOA, PFOS, PFNA and PFHxS, NHDES determined this novel and "fit-for-purpose" tool (Goeden et al., 2019) was necessary to evaluate exposure outcomes from the proposed MCLs. Specifically, the transfer of PFAS into breastmilk combined with the relatively high breastmilk and water ingestion rates of infants results in a prolonged elevation of serum levels throughout childhood. Under RME assumptions, the serum levels are predicted to be drastically higher than background serum levels seen in the general population, which is assumed to be free of widespread PFAS contamination in drinking water. Furthermore, this elevation throughout childhood into late adolescence limits the RSC allotment for exposure to other sources of PFAS in the environment that, to date, are not regulated.

The following subsections describe the inputs selected by NHDES for RME modeling using Goeden et al. (2019). A summary of model inputs, and associated references, used by NHDES for selection of the proposed MCLs are provided in Table 3.

Human half-life and V_d assumptions

Explanations of the selected half-lives for PFOA, PFOS, PFNA and PFHxS are described in the discussions of DAFs in Section III of this report. For PFOA, an average serum-based half-life was selected from Bartell et al. (2010), which was estimated from a sample population of 200 individuals from the Mid-Ohio valley who were exposed to PFOA from their drinking water supply due to contamination from a DuPont facility. NHDES selected the half-life estimates from Li et al. (2018) for PFOS and PFHxS. These serum-derived half-life estimates were determined to be more representative of the general population, and were obtained from a Swedish community (n = 106 participants) exposed to PFAS, namely PFOS and PFHxS, from drinking water contaminated by AFFF use at a nearby airbase (Li et al., 2018). Finally, the half-life estimate for PFNA was selected from Zhang et al. (2013) which reports urine-based values from a Chinese population (n = 86 participants).

Similar to the half-life values, the volume of distribution (V_d) estimates were identical to those selected by NHDES to derive RfDs for PFOA, PFOS, PFNA and PFHxS (Section III, and references therein).

Table 3. Exposure Model Parameters. Summary of parameters utilized in the transgenerational model (Goeden et al., 2019) by NHDES for derivation of proposed MCLs.

Model Parameter	Central or Upper Tendency of Parameter	PFOA	PFOS	PFHxS	PFNA
Half-Life, years (yrs)	Central	2.3 [a]	3.4 [b]	4.7 [b]	4.3 [c]
Placental Transfer Ratio	Central	0.72 [d]	0.40 [d]	0.70 [d]	0.69 [e]
Breastmilk Transfer Ratio	Central	0.050 [d]	0.017 [d]	0.014 [d]	0.032 [e]
Volume of Distribution (V_d), L/kg	Central	0.170 [f]	0.230 [f]	0.213 [g]	0.200 [e,h]
Relative Source Contribution (RSC), %	Central	50	50	50	50
		Same for All 4 PFAS Exposure Scenario Models			
Duration of Exclusive Breastfeeding, months	Upper	12			
Water Ingestion Rates, mL/kg-d [i] (EPA Exposure Factors Handbook, 2019 Update)					
Birth to <1 mon	Upper	224			
1 to <3 mons	Upper	267			
3 to <6 mons	Upper	158			
6 to <11 mons	Upper	133			
1 to <2 yrs	Upper	57			
2 to <3 yrs	Upper	67			
3 to <6 yrs	Upper	45			
6 to <11 yrs	Upper	41			
11 to <16 yrs	Upper	31			
16 to <18 yrs	Upper	31			
18 to <21 yrs	Upper	31			
21+ yrs	Upper	44			
Lactating Woman	Upper	47			
Breastmilk Ingestion Rates, mL/kg-d (EPA Exposure Factors Handbook, 2011)					
Birth to <1 mon	Upper	220			
1 to <3 mons	Upper	190			
3 to <6 mons	Upper	150			
6 to <12 mons	Upper	130			

[a] Bartell et al., 2010; [b] Li et al., 2018; [c] Zhang et al., 2013; [d] MDH, 2018, 2019ab
[e] MIDHHS, 2019; [f] Thompson et al., 2010; [g] Sundström et al., 2012; Ali et al., *in review*
[h] ATSDR, 2018b;
[i] Body weight and age-specific adjustments to the V_d were maintained the same as described in Goeden et al., 2019.

Placental & breastmilk transfer ratios

NHDES applied previously selected placental and breastmilk transfer ratios for PFOA (MDH 2018), PFOS (MDH 2019), PFNA (MIDHHS 2019) and PFHxS (MDH 2019). In line with the MDH and MIDHHS, NHDES opted to use central tendency values for each PFAS versus the upper or 95th percentile estimate for transfer in the RME scenarios (Table 3).

The exact quantitative nature of PFAS transfer across the placenta remains an active area of research. For example, Mamsen et al. (2019) demonstrated that the accumulation of PFAS in fetal tissues begins early in pregnancy and continues throughout gestation as specific PFAS are taken up by the forming organs with slightly different efficiencies. Several studies of cord blood compared to maternal serum levels of PFAS have been used to estimate placental transfer ratios and are used in the model to predict the "at birth" serum level (Fei et al., 2007; Midasch et al., 2007; Monroy et al., 2008; Fromme et al., 2010; Beesoon et al., 2011; Kim et al., 2011; Liu et al., 2011; Needham et al., 2011; Lee et al., 2013; Porpora et al., 2013; Kato et al., 2014; Cariou et al., 2015; Manzano-Salgado et al., 2015; Fisher et al., 2016; Yang et al., 2016; Chen et al., 2017; Mamsen et al., 2019). The average maternal-to-cord blood or placenta ratios ranged from 0.20 (Mamsen et al., 2019) to 1.24 (Midasch et al., 2007) for PFOA, 0.14 (Fisher et al., 2014) to 0.60 (Midasch et al., 2007) for PFOS, 0.24 (Mamsen et al., 2019) to 1.18 (Monroy et al., 2008) for PFNA, and 0.23 (Fisher et al., 2016) to 1.25 (Monroy et al., 2008) for PFHxS. A point of caution in interpreting placental transfer ratios in these studies is the trimester of pregnancy that data are collected. Changes in blood volume over the coruse of pregnancy are expected to affect the maternal blood concentration, thereby influences cord blood to maternal blood concentration ratios for various PFAS. Collectively, these studies provide valuable and reliable information for estimating the transfer from mother to newborn. This model does not predict fetal blood or tissue concentrations of PFAS as this compartmentalization is poorly understood, although recent work, such as Mamsen et al. (2019) may lead to the development of such models.

Compared to placental transfer efficiencies that are well-documented for PFAS, a small body of literature informs our understanding of the PFAS in breastmilk. As a part of its review of the technical documents described by MDH (2018, 2019ab) and MIDHHS (2019), NHDES reviewed the source papers for the breastmilk transfer ratios (Karrman et al., 2007; Haug et al., 2011; Kim et al., 2011; Liu et al., 2011; Cariou et al., 2015; Gyllenhammer et al., 2018). These studies demonstrate that the small average percentage (0.6-11% across various PFAS) transferred from a mother's serum, which is typically at concentrations of ng/mL or ppb, results in breastmilk at concentration ranges well above most existing drinking water advisories. Combined with relatively high ingestion rates of breastmilk relative to the infant's body weight, this results in a spike of infant blood concentrations that the model predicts will remain high through childhood.

Duration of breastfeeding

A major assumption for the breastfeeding component of this model is the duration of exclusive breastfeeding. Consistent with the RME scenarios selected by other states (MDH, 2018, 2019ab; MIDHHS, 2019), NHDES used a 12-month duration of *exclusive breastfeeding* for all four RME scenarios. Similar to the CDC, the World Health Organization (WHO) defines exclusive breastfeeding as:

> "Exclusive breastfeeding means that the infant receives only breast milk. No other liquids or solids are given – not even water – with the exception of oral rehydration solution, or drops/syrups of vitamins, minerals or medicines." – WHO eLENA (2019)

A central tendency assumption for the duration of exclusive breastfeeding would be 6 months, but NHDES selected a more conservative modeling parameter of 12 months of exclusive breastfeeding. A 12-month exclusive breastfeeding duration is a conservative assumption because the CDC recommends 6 months of exclusive breastfeeding and some continuation through infancy given the clear benefits to an infant's health and their long-term development. After 6 months of age, the recommendation is that other food items are introduced and breastfeeding continues for up to 2 years of age.

This assumption has been argued by some to be overly conservative relative to the RME scenarios as 1) CDC recommended exclusive breastfeeding for up to 6 months of age and 2) if an infant were exclusively breastfeeding at or after 12 months of age, it is unlikely they are not ingesting other fluids or foods. NHDES contends that this is a reasonable assumption given 1) the role that the duration of exclusive breastfeeding plays in the MN model and 2) the high rates of breastfeeding in New Hampshire and breastfeeding trends across the nation.

MDH notes that the duration of breastfeeding, along with breastmilk intake rates and water concentration, are the most sensitive parameters of the model (MDH 2017). The duration of exclusive breastfeeding and breastfeeding with complimentary foods varies, but the CDC recommends up to 2 years of breastfeeding with the addition of complimentary foods. The transgenerational model does not contain parameters for apportionment of exposure from breastmilk versus complimentary foods, or formula, across the first two years of life. Given this uncertainty for mixed exposures for breastfed infants, NHDES agreed that the assumption of a 12-month exclusive breastfeeding duration was appropriate for estimate for the purpose of the model.

Results from the National Immunization Survey (NIS) indicate that, in the general U.S. population of newborns, approximately 24.9% ± 1.2 (± half 95% CI) of infants are exclusively breastfed at 6 months of age. By 12 months, 35.9% ± 1.3 of infants consume breastmilk along with complimentary foods and liquids (CDC, 2018a). New Hampshire specific estimates from this same dataset are that 30.2% ± 5.8 of infants exclusively breastfeed at 6 months of age, while 45.6% ± 6.5 breastfeed at 12 months of age in addition to complimentary foods (CDC, 2018a). Based on the historical trends, the 2018 Breastfeeding Report Card (CDC, 2018b) indicates more women nationwide are breastfeeding or want to breastfeed their children, giving weight to the consideration of breastfeeding and selecting a conservative window of 12 months.

Breastmilk and drinking water ingestion rate assumptions

This transgenerational model evaluates the impact of changing water ingestion rates across a lifespan. These ingestion rates are expressed as liters of water per kilogram of an individual's body weight per day (L/kg-d). As a person grows, their physiological demand for water changes and this is reflected by age-specific ingestion rates, or life-process specific rates in the case of pregnant and lactating women. To put this in context of historical practice, the EPA typically assumed a drinking water ingestion rate of 2 L/d

for adults and 1 L/d for infants and children under 10 years of age (U.S. EPA, 2000). After adjusting for body weight, these typical rates would underestimate the water consumption of infants, children and lactating and pregnant women. Thus, consideration of these life-stage specific values is prudent for a persistent and highly-bioaccumulative class of drinking water contaminants.

To be protective of the general population including high-end water consumers, NHDES applied the 95th percentile water and breastmilk ingestion rates throughout life in the RME scenarios for PFOA, PFOS, PFHxS and PFNA. The use of the 95th percentile for water ingestion rates is consistent with the initial proposal, and this is simply an extension to other life stages. Recently updated values in 2019 Updated Chapter 3 of the Exposure Factors Handbook (EPA, 2019) were combined with estimated breastmilk ingestion rates from Chapter 15 of the 2011 Edition (EPA, 2011). As these changes were specific to water ingestion, not breastmilk, the difference between the 2011 and 2019 estimates for infants, a change of -9% to +3% for those <1 year of age, was determined to be a minor and tolerable change to the RME scenarios. The breastfed RME exposure was the driver of the MCL for all evaluated PFAS, and therefore protective of an individual in the formula-fed RME scenario.

Consideration of the Relative Source Contribution (RSC)

Exposure to PFAS is not solely due to drinking water, so in order for the MCL to be health protective NHDES needs to account for the contribution of other sources towards the reference dose (RfD). The proportion of exposure attributed to a specific source is accounted for through the relative source contribution (RSC). With respect to a MCL, the RSC is the percentage of total exposure typically accounted for by drinking water (EPA 2000). This value can be referred to as a proportion or percentage, and EPA recommends a ceiling of 80% and a floor of 20%. A smaller RSC for drinking water exposure results in a lower regulatory standard, but implies that sources other than water contribute more significantly to exposure.

Presently, there is no inventory of all relevant sources of PFAS exposure to determine what proportion each source shares in an RSC for the general population. Several studies have characterized specific media such as dust, food (Kowalczyk et al., 2013; reviewed by EFSA, 2018) and breastmilk (previously discussed) and estimated the percentages of total exposure attributable to these sources; but no single study has merged these findings to estimate the reasonable and realistic RSC for drinking water.

In the absence of such data, the EPA provides a decision tree for identifying an appropriate RSC (replicated in Figure 1; EPA 2000). Following this process, NHDES determined:

- (Box 6 to 8a) *Yes, there are significant known sources of these PFAS other than drinking water*. As a result of their dispersion into the environment and lack of adequate removal from waste streams, there are known sources of PFAS that contribute to environmental exposures. This includes release into surface water and implications for fish and shellfish consumption (Fair et al., 2019), and the impacts of PFAS contamination of soil (Filipovic et al., 2015; Scher et al., 2018), dust (Fu et al., 2015; Winkens et al., 2018) and agriculture-related exposures (Nascimento et al., 2018; reviewed by Ghisi et al., 2019).

- (Box 8a to 8c) *Yes, there is some information to make a characterization of exposure*. As mentioned above, there is some data on environmental sources to make rough characterizations. Additionally, there is blood data from the National Health and Nutrition Examination Survey (NHANES) to estimate the general exposure of the U.S. population to PFAS. The NHANES data for blood levels of PFAS is assumed to reflect general exposure to all sources in the U.S. population, and is presumed to not reflect the results of excessively high exposures, relative to the proposed MCLs, due to contaminated drinking water as seen in the communities of Southern New Hampshire Pease Tradeport and Southern New Hampshire.
- (Box 8c to 13) *NHDES performed apportionment with a 50% ceiling and 20% floor for each of the assessed PFAS*. This apportionment was achieved using the EPA subtraction method (EPA 2000).

The subtraction method (EPA 2000) estimates an apportionment of the RSC is based on assumed knowledge of the background exposure. For PFAS, the subtraction method has been mathematically applied as follows (NJDWQI 2018; MDH 2018, 2019ab):

$$\text{Relative Source Contribution} = \frac{\text{Target serum level } \left(\frac{\text{ng}}{\text{mL}}\right) - \text{Reference or background population level } \left(\frac{\text{ng}}{\text{mL}}\right)}{\text{Target serum level } \left(\frac{\text{ng}}{\text{mL}}\right)} \times 100\%$$

The difference between the target serum level and the RfD is that the former is an internal blood concentration while the latter is the external amount of the chemical that could come from multiple sources. For each of the compounds, the target serum levels were: PFOA – 43.5 ng/mL, PFOS – 23.6 ng/mL, PFNA – 49.0 ng/mL and PFHxS – 46.3 ng/mL. The reference population serum level is meant to reflect a background level of exposure from the general population, not one that is highly exposed due to a specific environmental source such as drinking water. Using the NHANES average serum values, subtracting this background level from the target serum level (the maximum allowable level) results in a proportion that is presumably permissible for drinking water alone. Other sources including food, dust, treated consumer products (e.g., carpeting, cookware, food packaging, etc.) are assumed to be included in the reference or background population blood concentrations.

Using this approach with the NHANES 2013-2014 data for children ranging in age from 3 to 19 years (as reported in Daly et al., 2018), NHDES arrived at RSCs of 50% for PFOA, PFOS, PFNA and PFHxS. Unlike its initial proposal, NHDES selected the NHANES dataset over the use of NH-specific estimates. The NH-specific blood data was focused on communities whose primary exposure was associated with drinking water, and would therefore overestimate non-drinking water exposure sources if used to establish an RSC as initially proposed in January (NHDES, 2019). Thus, the NHANES dataset was deemed more appropriate to account for other non-drinking water sources of exposure. For an understanding of how the NHANES data compares to that collected from one of the highly-exposed communities in New Hampshire and the limitations of interpreting these findings, readers are referred to Daly et al. (2018).

Instead of using the general population (i.e., all ages), NHDES estimated RSCs based on the serum concentrations from those younger than 19 years of age (Table 4). As emphasized in several comments made to NHDES on its initial proposal, the risk assessment needs to consider current information for children. Since the phase out of certain PFAS, but not all, the national average serum levels have declined suggesting some reduction of background exposure. Given the emphasis of the RME on infancy

and early childhood, NHDES determined it was appropriate to derive the RSC with specific consideration of this group. All of the values for PFOA, PFOS, PFNA and PFHxS were at or above 48.3%, therefore NHDES opted for an RSC of 50%.

NHDES acknowledges that the use of the general NHANES estimates that includes adults with historically high exposures results in similar or more restrictive RSC values; especially for PFOS. However, the RME scenarios for the proposed MCLs indicate that the predicted serum level for the 95th percentile of adult water consumers is approximately equal to or below the 20% RSC and therefore sufficiently protective after considering the context of the national dataset. Furthermore, the cap of 50% despite calculated higher RSCs for each of these accounts for the unknown and novel sources of PFAS exposure, as well as the higher serum levels of PFAS found in New Hampshire's highly-exposed communities.

Table 4. Relative Source Contribution Estimates. Various relative source contribution (RSC) values resulting from use of the EPA subtraction method (EPA 2002) in combination with available serum data for the geometric mean (GM) and 95th percentile from the NHANES 2013-2014 dataset, as reported in Daly et al. (2018).

Reference Population	Reference Serum level (ng/mL)	Target Serum Level (ng/mL)	Resulting RSC Allotment for Drinking Water (%)
PFOA			
3-5 year olds (GM)	2.00	43.5	95.4
6-11 year olds (GM)	1.89	43.5	95.7
12-19 year olds (GM)	1.66	43.5	96.2
3-5 year olds (95th percentile)	5.58	43.5	87.2
6-11 year olds (95th percentile)	3.84	43.5	91.2
12-19 year olds (95th percentile)	3.47	43.5	92.0
PFOS			
3-5 year olds (GM)	3.38	24.0	85.9
6-11 year olds (GM)	4.15	24.0	82.7
12-19 year olds (GM)	3.54	24.0	85.3
3-5 year olds (95th percentile)	8.82	24.0	63.3
6-11 year olds (95th percentile)	12.40	24.0	48.3
12-19 year olds (95th percentile)	9.30	24.0	61.3
PFNA			
3-5 year olds (GM)	0.76	49.0	98.4
6-11 year olds (GM)	0.81	49.0	98.3
12-19 year olds (GM)	0.60	49.0	98.8
3-5 year olds (95th percentile)	3.49	49.0	92.9
6-11 year olds (95th percentile)	3.19	49.0	93.5
12-19 year olds (95th percentile)	2.00	49.0	95.9
PFHxS			
3-5 year olds (GM)	0.72	46.3	98.4
6-11 year olds (GM)	0.91	46.3	98.0
12-19 year olds (GM)	1.27	46.3	97.3
3-5 year olds (95th percentile)	1.62	46.3	96.5
6-11 year olds (95th percentile)	4.14	46.3	91.1
12-19 year olds (95th percentile)	6.30	46.3	86.4

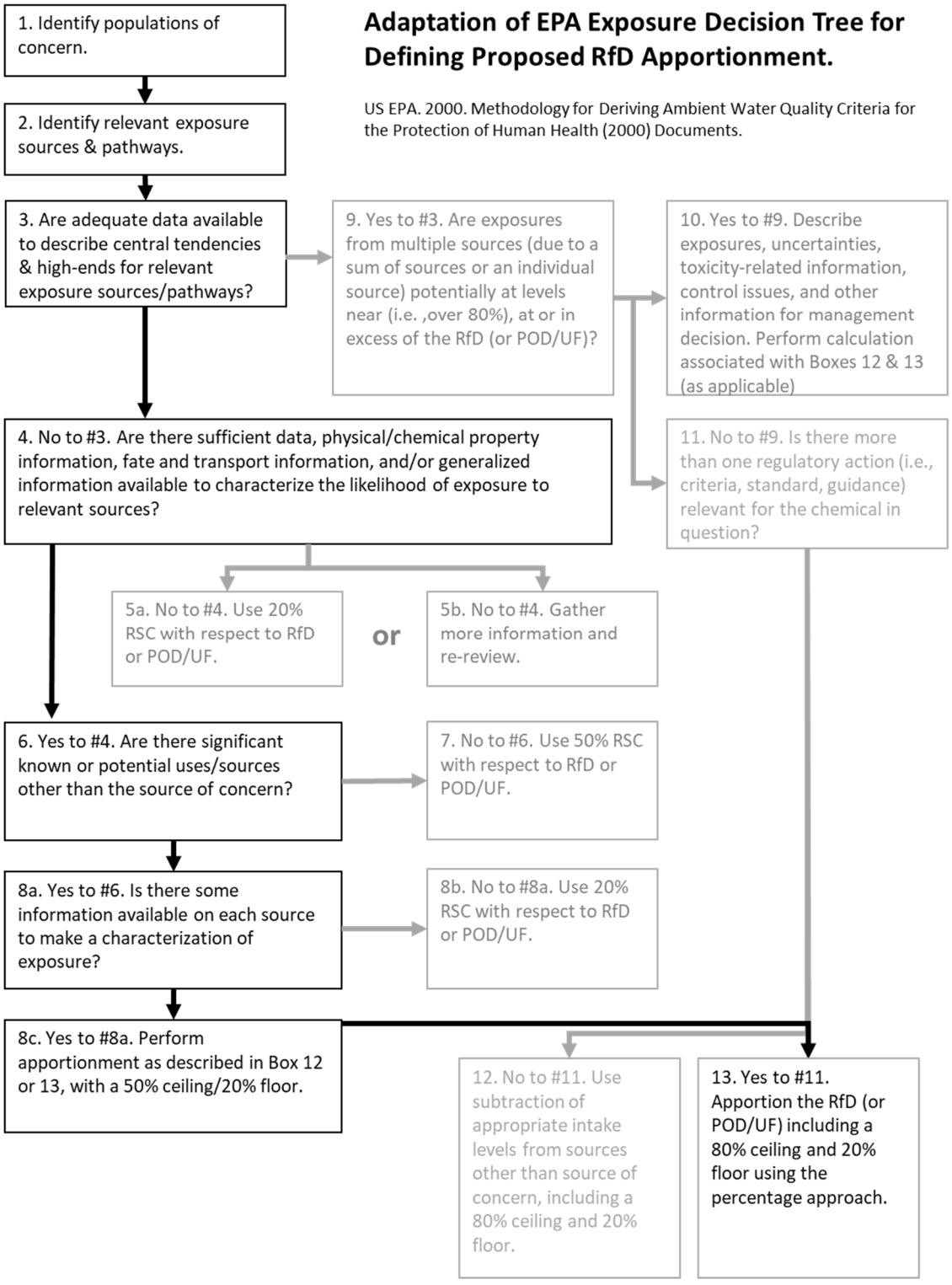


Figure 1. Adaptation of EPA decision tree (EPA, 2000) for determining the RSC. Black boxes, text and arrows outline the decision process used by NHDES to arrive at the subtraction method for PFAS with a 50% ceiling. The target serum level is a population assessment value, *not clinical*, from the derivation of the RfDs, detailed in Section III.

Section V. Discussion of the MCLs proposed by NHDES

Based on the previously described RfDs, exposure considerations and application of the transgenerational model (Figure 2), the proposed maximum contaminant levels (MCLs) are:

- **12 ng/L for Perfluorooctanoic acid, or perfluorooctanoate (PFOA)**
- **15 ng/L for Perfluorooctane sulfonic acid, or perfluorooctane sulfonate (PFOS)**
- **11 ng/L for Perfluorononanoic acid, or perfluorononanoate (PFNA)**
- **18 ng/L for Perfluorohexane sulfonic acid, or perfluorohexane sulfonate (PFHxS)**

These health-based values are intended as health-protective limits against the chronic health effects for a through-life exposure. The primary associated health outcomes are hepatotoxicity and changes in lipid metabolism (PFOA and PFNA), suppressed immune response to vaccines (PFOS) and impaired female fertility (PFHxS). Secondary associated health effects that are expected to be less sensitive are changes in thyroid and sex hormone levels, early-life growth delays, changes in cholesterol levels and biomarkers of liver function, neurobehavioral effects, and a possible risk for certain cancers (i.e., testicular and kidney).

Modeled Exposure Results

Figure 2 shows the model result for predicted serum concentrations at the proposed MCL for each PFAS. The exposure starts at birth with the assumption that the mother is at a steady-state serum level from consumption of water at the modeled drinking water concentration. The solid blue line represents the highest exposure in the RME model, showing the predicted serum level for a breastfed infant who consumes breastmilk and water at the 95th percentile ingestion rates throughout life and is born to and breastfeeds from a mother with a similar water consumption rate. The solid green line represents the predicted serum level for a formula-fed infant who consumes formula (reconstituted with water at the MCL) and water at the 95th percentile ingestion rates throughout life and is born to a mother with a similar water consumption rate. The dashed lines represent the predicted serum concentrations for individuals at the central tendency or average breastmilk, formula and water ingestion rates.

There is a clear spike in predicted serum levels of breastfed infants due to the aforementioned transfer efficiencies of PFAS into breastmilk. For infants, this is concerning due to the potential for hand-to-mouth behaviors in later infancy that have been shown to contribute to PFAS exposure in children of this age (Trudel et al., 2008). Because of these potential exposures and the suspected health impacts on early development, NHDES selected an MCL value that does not allow the predicted infant serum level to exceed the 50% RSC of the RfD or target serum level. It is true that the central tendency consumers fall well below this threshold. However, it has been shown that when considering variants on the RME scenarios the use of the 95th percentile ingestion rate is adequately protective for other factors (e.g., higher breastmilk transfer efficiencies or longer half-life estimates) (Goeden et al., 2019).

The long half-lives of these compounds result in significantly elevated serum levels peaking at the cessation of breastfeeding and continuing through the remainder of childhood. While the predicted steady-state concentrations for adults or formula-fed infants would allow less restrictive MCLs, breastfed children could potentially exceed the RfD due to other sources such as dust (Winkens et al., 2018) or foods and food packaging (D'eon et al., 2009; reviewed by EFSA, 2018). This point further emphasizes the appropriateness of the 50% cap on the RSC as selected by NHDES.

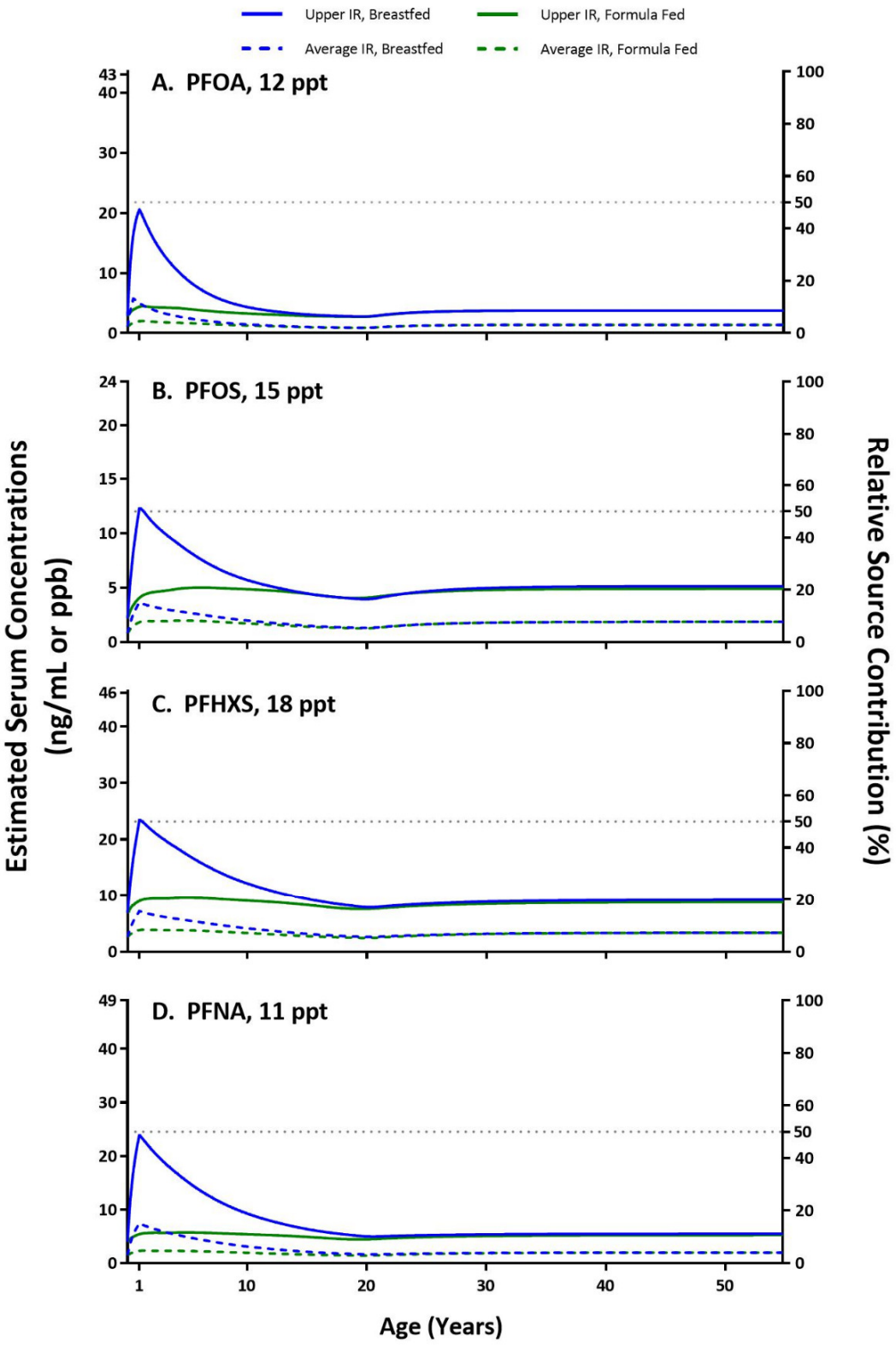


Figure 2. Predicted serum PFAS concentrations in response to upper (95th percentile) and average (mean) water ingestion rates (IR) at the proposed MCLs. Blue lines indicate results for breastfed infants with 12 months exclusive breastfeeding, and green lines indicate results for formula-fed infants. Solid lines represent upper IRs and dashed lines indicate average (mean) IRs. Estimates made using the model described in Goeden et al. (2019).

Using the proposed MCL values for each compound, serum concentrations attributable to drinking water can be estimated for an individual across various life stages (adapted from Figure 2). For newborns (at birth), the estimated drinking water contribution to serum concentrations for the 95th percentile consumer would be: 2.9 ng/mL for PFOA, 2.2 ng/mL for PFOS, 4.0 ng/mL for PFNA and 6.9 ng/mL for PFHxS. The model does not predict fetal tissue concentrations, so the predicted at-birth values represent the aforementioned placental transfer efficiencies. The predicted drinking water contribution to serum concentrations for the 95th percentile breastmilk consumer (at the end of 1 year of exclusive breastfeeding) would be: 20.6 ng/mL for PFOA, 12.4 ng/mL for PFOS, 25.1 ng/mL for PFNA and 23.5 ng/mL for PFHxS. Adults at steady state following constant water consumption at the 95th percentile are predicted to have drinking water contributions of PFAS equal to or less than: 3.8 ng/mL for PFOA, 5.1 ng/mL for PFOS, 5.7 ng/mL for PFNA and 9.2 ng/mL for PFHxS.

As a point of caution in interpretation, the previously described results assume no fluctuation from the 95th percentile drinking water consumption rate across an individual lifespan. That is to say, the 95th percentile consumer remains the 95th percentile consumer every day. These estimates include several conservative and protective assumptions, such as the use of the 95th percentile of drinking water ingestion rates (adjusted for body weight) throughout life, not the average water consumer or fluctuations between these tendencies. Additionally, the modeled outputs may not reflect individual variations in biology throughout life (Fàbrega et al., 2014; Worley et al., 2017) and are intended for population-level exposure assessment. However, as described by Goeden et al. (2019), this fit-for-purpose tool provides important insight into exposures during critical life stages of development. Further development and refinement of multi-compartment models will certainly prove useful for future risk assessments of these and other PFAS.

The proposed MCLs are predicted to result in a modest increase of serum concentrations due to drinking water levels; but, as argued by Post et al. (2017), such increases relative to background are preferred over the significantly larger serum levels that are predicted for the previously proposed MCLs (NHDES, 2019) or the EPA lifetime health advisories (EPA, 2016ab). Based on current evidence, this level of exposure is expected to be sufficiently health protective relative to current background levels reported in populations of concern, such as children and adolescents (Table 4).

Limitations and uncertainties

As with any risk assessment, this process was subject to uncertainty and limitations. Limitations included recommendation of individual versus group-based MCLs for PFAS, and consideration of background exposure using the RME scenarios described in Section IV. A major uncertainty was quantifying the exact risks of disease incidence for each compound, which is also a significant challenge for quantifying, or monetizing, the benefits of the proposed MCLs.

A limitation to the present assessment is that the transgenerational model's RME scenarios focus on the predicted impact of drinking water exposure, not other background sources of exposure. In general, there is a downward trend for the background levels of most measured PFAS based on the NHANES data. NHDES considered this with its use of the NHANES data to derive and apply a 50% RSC for each compound. Although PFOA and PFOS were recently phased out by most U.S. manufacturers, there remains potential for exposure to these and other PFAS from imported products or the degradation of

precursors into PFOA or PFOS in the environment. Nevertheless, the appropriate level of conservatism applied in the assumptions of drinking water ingestion rates and RSC provide reasonable protection.

At this time, NHDES is not recommending a class-based approach to regulation of these compounds. This is a limitation of the present risk assessment given the considerable number of PFAS detected in the environment and used in commerce. However, individual assessment of each compound found each one to have relatively unique toxico-dynamic and –kinetic properties based on consideration of existing animal toxicity and human data. Despite similarity in the range of the proposed MCLs for these 4 PFAS, it is likely that future individual assessments, using current EPA methodology, of shorter carbon chain PFAS will result in higher drinking water values for shorter carbon chain compounds as a result of shorter half-lives. Given these considerations, it was determined that a class based approach was not advisable at this time. Should other state agencies or the U.S. EPA identify science-based methods for group regulation that account for some of the unique properties of these compounds, NHDES will consider this approach.

Currently, there is uncertainty to quantifying the health risks associated with exposure to PFOA, PFOS, PFNA, PFHxS and other PFAS. A growing number of epidemiological and animal toxicity studies are adding to the body of evidence for the biological activity and health outcomes associated with these contaminants. However, the exact nature of PFAS-related health hazards remains elusive due to a variety of factors including, but not limited to: a limited understanding of the toxicological mechanism of action, their occurrence world-wide and lack of control (i.e., PFAS-free) populations to compare health outcomes against, lack of long-term studies despite decades of use, and co-exposure with other PFAS and other environmental contaminants. Additional research is critically needed to address this issue and better characterize and quantify the risks associated with PFAS.

Conclusions

The lower MCLs proposed in this report are primarily due to consideration of the elevated serum levels predicted for infants and young children under a reasonable maximum exposure scenario. At the initially proposed values, these spikes in infant blood levels of PFAS would result in unacceptable reductions in the margin of exposure from infancy through childhood due to the unique properties of PFAS. Their capacity to transfer through breastmilk combined with relatively long half-lives of each compound merits the use of novel methods (i.e., Goeden et al., 2019) to provide a more accurate assessment of exposure. This is not a recommendation against breastfeeding for women who are currently breastfeeding or plan to breastfeed as the benefits of breastfeeding are very well-defined relative to the potential risk associated with PFAS. NHDES recommends these MCLs to afford adequate long-term health protection of the population based on its assessment of these four PFAS.

The human health impacts of PFAS is a continuously evolving area of scientific research, and is expected to continue changing in the future. The assessments made by NHDES are based on currently available information but recognizes that science is a process, not an outcome. Future assessments of these and other PFAS compounds may result in higher or lower health protective values based on the best available science at the time. NHDES will continue to review emerging information as a part of its ongoing efforts to understand the impacts of PFAS contamination across New Hampshire.

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2018a. Toxic Substances Portal: Minimal Risk Levels (MRLs) – For Professionals. Updated June 21, 2018. https://www.atsdr.cdc.gov/mrls/index.asp

Agency for Toxic Substances and Disease Registry (ATSDR). 2018b. Toxicological Profile for Perfluoroalkyls – Draft for Public Comment, June 2018. Accessed online at: https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf.

Albrecht PP, Torsell NE, Krishnan P, et al. 2013. A species difference in the peroxisome proliferator-activated receptor α-dependent response to the developmental effects of perfluorooctanoic acid. Toxicol Sci 131(2):568-582.

Ali JM, Roberts SM, Gordon DS, Stuchal LD. (in review) Derivation of a chronic reference dose for perfluorohexane sulfonate (PFHxS) for reproductive toxicity in mice.

Ballesteros V, Costa O, Iñiguez C, Fletcher T, Ballester F, Lopez-Espinosa MJ. 2017. Exposure to perfluoroalkyl substances and thyroid function in pregnant women and children: A systematic review of epidemiologic studies. Environ Int, 99:15-28. doi: 10.1016/j.envint.2016.10.015.

Bartell SM, Calafat AM, Lyu C, et al. 2010. Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. Environ Health Perspect 118(2):222-228

Barry V, Winquist A, Steenland K. 2013. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. Environ Health Perspect 121(11-12):1313-1318.

Bassler J, Ducatman A, Elliott M, Wen S, Wahlang B, Barnett J, Cave MC. 2019. Environmental perfluoroalkyl acid exposures are associated with liver disease characterized by apoptosis and altered serum adipocytokines. Environ Pollut. 247:1055-1063. doi: 10.1016/j.envpol.2019.01.064

Beesoon S, Webster GM, Shoeib M, Harner T, Benskin JP, Martin JW. 2011. Isomer profiles of perfluorochemicals in matched maternal, cord, and house dust samples: manufacturing sources and transplacental transfer. Environ Health Perspect. 119(11):1659-64. doi: 10.1289/ehp.1003265.

Bijland S, Rensen PC, Pieterman EJ, et al. 2011. Perfluoroalkyl sulfonates cause alkyl chain length-dependent hepatic steatosis and hypolipidemia mainly by impairing lipoprotein production in APOE*3-Leiden CETP mice. Toxicol Sci 123(1):290-303. 10.1093/toxsci/kfr142.

Boronow KE, et al. 2019. Serum concentrations of PFASs and exposure-related behaviors in African American and non-Hispanic white women. Journal of Exposure Science & Environmental Epidemiology, pp. 1-12.

Butenhoff J, Costa G, Elcombe C, et al. 2002. Toxicity of ammonium perfluorooctanoate in male Cynomolgus monkeys after oral dosing for 6 months. Toxicol Sci 69(1):244-257.

Butenhoff JL, Chang S, Ehresman DJ, et al. 2009a. Evaluation of potential reproductive and developmental toxicity of potassium perfluorohexanesulfonate in Sprague Dawley rats. Reprod Toxicol 27:331-341.

Butenhoff JL, Ehresman DJ, Chang SC, et al. 2009b. Gestational and lactational exposure to potassium perfluorooctanesulfonate (K+PFOS) in rats: Developmental neurotoxicity. Reprod Toxicol 27(3-4):319-330.

Butenhoff JL, et al. 2008. Evaluation of potential reproductive and developmental toxicity of potassium perfluorohexanesulfonate in Sprague Dawley rats. Reproductive Toxicology, 27, 331-341.

Butenhoff, J.L., G.L. Kennedy, Jr., S.-C. Chang, and G.W. Olsen. 2012. Chronic dietary toxicity and carcinogenicity study with ammonium perfluorooctanoate in Sprague-Dawley rats. Toxicology 298:1–13.

Butenhoff, J.L., G.L. Kennedy, S.R. Frame, J.C. O'Conner, and R.G. York. 2004. The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. Toxicology 196:95–116.

California Office of Environmental Health Hazard Assessment. 2019. PFOA and PFOS Notification Levels. https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/PFOA_PFOS.html

Cariou R, Veyrand B, Yamada A, et al. 2015. Perfluoroalkyl acid (PFAA) levels and profiles in breast milk, maternal and cord serum of French women and their newborns. Environ Int 84:71-81.

Chang ET, et al. 2016. A critical review of perfluorooctanoate and perfluorooctanesulfonate exposure and immunological health conditions in humans. Crit Rev Toxicol., 46(4): 279-331.

Chang S, et al. 2018. Reproductive and developmental toxicity of potassium perfluorohexanesulfonate in CD-1 mice. Reproductive Toxicology 78: 150-168.

Chen F, Yin S, Kelly BC, Liu W. 2017. Isomer-Specific Transplacental Transfer of Perfluoroalkyl Acids: Results from a Survey of Paired Maternal, Cord Sera, and Placentas. Environ Sci Technol. 51(10):5756-5763. doi: 10.1021/acs.est.7b00268.

Cheng J, Fujimura M, Zhao W, et al. 2013. Neurobehavioral effects, c-Fos/Jun expression and tissue distribution in rat offspring prenatally co-exposed to MeHg and PFOA: PFOA impairs Hg retention. Chemosphere 91(6):758-764.

Cui L, Zhou QF, Liao CY, et al. 2009. Studies on the toxicological effects of PFOA and PFOS on rats using histological observation and chemical analysis. Arch Environ Contam Toxicol 56(2):338-349.

Cui Y, et al. 2015. Investigation of the Effects of Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS) on Apoptosis and Cell Cycle in a Zebrafish (Danio rerio) Liver Cell Line. Int J Environ Res Public Health. 12(12):15673-82.

Daly ER, Chan BP, Talbot EA, Nassif J, Bean C, Cavallo SJ, Metcalf E, Simone K, Woolf AD. 2018. Per- and polyfluoroalkyl substance (PFAS) exposure assessment in a community exposed to contaminated drinking water, New Hampshire, 2015. Int J Hyg Environ Health. 221(3):569-577. doi: 10.1016/j.ijheh.2018.02.007.

Das KP, Grey BE, Rosen MB, et al. 2015. Developmental toxicity of perfluorononanoic acid in mice. Reprod Toxicol 51:133-144. 10.1016/j.reprotox.2014.12.012.

Das KP, Wood CR, Lin MT, et al. 2017. Perfluoroalkyl acids-induced liver steatosis: Effects on genes controlling lipid homeostasis. Toxicology 378:37-52. 10.1016/j.tox.2016.12.007.

D'eon JC, Crozier PW, Furdui VI, Reiner EJ, Libelo EL, Mabury SA. 2009. Observation of a commercial fluorinated material, the polyfluoroalkyl phosphoric acid diesters, in human sera, wastewater treatment plant sludge, and paper fibers. Environ. Sci. Technol. 43: 4589-4594.

DeWitt JC, Blossom SJ, Schaider LA. 2019. Exposure to per-fluoroalkyl and polyfluoroalkyl substances leads to immunotoxicity: epidemiological and toxicological evidence. J Expo Sci Environ Epidemiol. 29(2):148-156. doi: 10.1038/s41370-018-0097-y

DeWitt JC, Peden-Adams MM, Keller JM, Germolec DR. 2012. Immunotoxicity of Perfluorinated Compounds: Recent Developments. Toxicologic Pathology, 40: 300-311.

Dong GH, Liu MM, Wang D, et al. 2011. Sub-chronic effect of perfluorooctanesulfonate (PFOS) on the balance of type 1 and type 2 cytokine in adult C57BL6 mice. Arch Toxicol 85(10):1235-1244.

Dong GH, Zhang YH, Zheng L, et al. 2009. Chronic effects of perfluorooctanesulfonate exposure on immunotoxicity in adult male C57BL/6 mice. Arch Toxicol 83(9):805-815.

Elcombe CR, Elcombe BM, Foster JR, et al. 2010. Hepatocellular hypertrophy and cell proliferation in Sprague-Dawley rats following dietary exposure to ammonium perfluorooctanoate occurs through increased activation of the xenosensor nuclear receptors PPARα and CAR/PXR. Arch Toxicol 84(10):787-798.

Ernst A, Brix N, Lauridsen LLB, Olsen J, Parner ET, Liew Z, Olsen LH, Ramlau-Hansen CH. 2019. Exposure to Perfluoroalkyl Substances during Fetal Life and Pubertal Development in Boys and Girls from the Danish National Birth Cohort. Environ Health Perspect. 127(1):17004. doi: 10.1289/EHP3567.

European Food Safety Authority (EFSA). 2018. Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. EFSA Journal, 16(12):5194

Fàbrega F, Kumar V, Schuhmacher M, Domingo JL, Nadal M. 2014. PBPK modeling for PFOS and PFOA: validation with human experimental data. Toxicol Lett. 230(2):244-51. doi: 10.1016/j.toxlet.2014.01.007.

Fair PA, Wolf B, White ND, Arnott SA, Kannan K, Karthikraj R, Vena JE. 2019. Perfluoroalkyl substances (PFASs) in edible fish species from Charleston Harbor and tributaries, South Carolina, United States: Exposure and risk assessment. Environ Res. 171:266-277. doi: 10.1016/j.envres.2019.01.021

Fang X, Fenga Y, Wang J, et al. 2010. Perfluorononanoic acid-induced apoptosis in rat spleen involves oxidative stress and the activation of caspase-independent death pathway. Toxicology 267: 54-59

Fei C, McLaughlin JK, Tarone RE, et al. 2007. Perfluorinated chemicals and fetal growth: A study within the Danish National Birth Cohort. Environ Health Perspect 115:1677-1682.

Filipovic M., Woldegiorgis A., Norström K., Bibi M., Lindberg M., Österås A.H. Historical usage of aqueous film forming foam: A case study of the widespread distribution of perfluoroalkyl acids from a military airport to groundwater, lakes, soils and fish. Chemosphere. 2015;129:39–45. doi: 10.1016/j.chemosphere.2014.09.005

Fisher M, Arbuckle TE, Liang CL, et al. 2016. Concentrations of persistent organic pollutants in maternal and cord blood from the maternal-infant research on environmental chemicals (MIREC) cohort study. Environ Health 15(1):59.

Fromme H, Mosch C, Morovitz M, et al. 2010. Pre- and postnatal exposure to perfluorinated compounds (PFCs). Environ Sci Technol 44(18):7123-7129.

Fu J, Gao Y, Wang T, Liang Y, Zhang A, Wang Y, Jiang G. 2015. Elevated levels of perfluoroalkyl acids in family members of occupationally exposed workers: the importance of dust transfer. Sci Rep. 20;5:9313. doi: 10.1038/srep09313.

Ghisi R, Vamerali T, Manzetti S. 2019. Accumulation of perfluorinated alkyl substances (PFAS) in agricultural plants: A review. Environ Res. 169:326-341. doi: 10.1016/j.envres.2018.10.023.

Gleason JA, Post GB, Fagliano JA. 2015. Associations of perfluorinated chemical serum concentrations and biomarkers of liver function and uric acid in the US population (NHANES), 2007-2010. Environ Res 136:8-14. 10.1016/j.envres.2014.10.004.

Goeden HM, Greene CW, Jacobus JA. 2019. A transgenerational toxicokinetic model and its use in derivation of Minnesota PFOA water guidance. J Expo Sci Environ Epidemiol. 29(2):183-195. doi: 10.1038/s41370-018-0110-5.

Grandjean P, et al. 2012. Serum Vaccine Antibody Concentrations in Children Exposed to Perfluorinated Compounds. JAMA, 307(4): 391-397.

Grandjean P, Landrigan PJ. (2014). Neurobehavioural effects of developmental toxicity. Lancet Neurol . 13, 330–338.

Gyllenhammar I, Benskin JP, Sandblom O, Berger U, Ahrens L, Lignell S, Wiberg K, Glynn A. 2018. Perfluoroalkyl Acids (PFAAs) in Serum from 2-4-Month-Old Infants: Influence of Maternal Serum Concentration, Gestational Age, Breast-Feeding, and Contaminated Drinking Water. Environmental Science and Technology. 2018 Jun 19;52(12):7101-7110. doi: 10.1021/acs.est.8b00770

Hagenaars A, et al. 2013. Mechanistic toxicity study of perfluorooctanoic acid in zebrafish suggests mitochondrial dysfunction to play a key role in PFOA toxicity. Chemosphere, 91(6): 844-56.

Hall AP, Elcombe CR, Foster JR, et al. 2012. Liver hypertrophy: A review of adaptive (adverse and non-adverse) changes- conclusions from the 3rd International ESTP Expert Workshop. Toxicol Pathol 40:971-994.

Haug LS, et al. 2011. Investigation on Per- and Polyfluorinated Compounds in Paired Samples of House Dust and Indoor Air from Norwegian Homes. Environmental Science & Technology, 45, 7991-7998.

Haug LS. 2011. Characterisation of human exposure pathways to perfluorinated compounds – comparing exposure estimates with biomarkers of exposure. Dissertation for the degree of Doctor of Philosophiae, University of Oslo.

Haug, L.S., Huber, S., Becher, G., Thomsen, C. 2011. Characterisation of human exposure pathways to perfluorinated compounds - comparing exposure estimates with biomarkers of exposure. Environ. Int. 37: 687-693.

Health Canada. 2016a. Perfluorooctanoic acid (PFOA) in drinking water. Available online at: https://www.canada.ca/content/dam/hc-sc/healthy-canadians/migration/health-system-systeme-sante/consultations/acide-perfluorooctanoic-acid/alt/perfluorooctanoic-eng.pdf

Health Canada. 2016b. Perflurooctane sulfonate (PFOS) in drinking water. Available online at: https://www.canada.ca/content/dam/hc-sc/healthy-canadians/migration/health-system-systeme-sante/consultations/perfluorooctane-sulfonate/alt/perfluorooctane-sulfonate-eng.pdf

Hu Q, Strynar MJ, DeWitt JC. 2010. Are developmentally exposed C57BL/6 mice insensitive to suppression of TDAR by PFOA? J Immunotoxicol 7(4):344-349.

International Agency for Research on Cancer (IARC) 2016: CAS No. 335-67-1, Agent = Perfluorooctanoic acid (PFOA) Group 2B, Volume 110, 2016 online, Available at: http://monographs.iarc.fr/ENG/Classification/latest_classif.php

Jain RB, Ducatman A. 2019. Selective Associations of Recent Low Concentrations of Perfluoroalkyl Substances with Liver Function Biomarkers: NHANES 2011 to 2014 Data on US Adults Aged ≥20 Years. J Occup Environ Med. 61(4):293-302.

Kang H, et al. 2016. Elevated levels of short carbon-chain PFCAs in breast milk among Korean women: Current status and potential challenges. Environmental Research, 148, 351-359.

Kärrman A, Ericson I, van Bavel B, et al. 2007. Exposure of perfluorinated chemicals through lactation: Levels of matched human milk and serum and a temporal trend, 1996-2004, in Sweden. Environ Health Perspect 115:226-230.

Kato K, Wong LY, Chen A, et al. 2014. Changes in serum concentrations of maternal poly- and perfluoroalkyl substances over the course of pregnancy and predictors of exposure in a multiethnic cohort of Cincinnati, Ohio pregnant women during 2003-2006. Environ Sci Technol 48(16):9600-9608.

Kim D-H, et al. 2019. Assessment of individual-based perfluoroalkyl substances exposure by multiple human exposure sources. Journal of Hazardous Materials, 365, 26-33.

Kim SK, Lee KT, Kang CS, et al. 2011. Distribution of perfluorochemicals between sera and milk from the same mothers and implications for prenatal and postnatal exposures. Environ Pollut 159(1):169-174.

Kirk M, Smurthwaite K, Bräunig J et al. (2018). The PFAS Health Study: Systematic Literature Review. Canberra: The Australian National University.

Klaunig JE, Hocevar BA, Kamendulis LM. 2012. Mode of action analysis of perfluorooctanoic acid (PFOA) tumorigenicity and human relevance. Reprod Toxicol 33(4):410-418.

Koskela A, Finnila MA, Korkalainen M, et al. 2016. Effects of developmental exposure to perfluorooctanoic acid (PFOA) on long bone morphology and bone cell differentiation. Toxicol Appl Pharmacol 301:14-21. 10.1016/j.taap.2016.04.002.

Koustas E, Lam J, Sutton P, et al. 2014. The Navigation Guide - evidence-based medicine meets environmental health: Systematic review of nonhuman evidence for PFOA effects on fetal growth. Environ Health Perspect 122(10):1015-1027.

Kowalczyk J., Ehlers S., Oberhausen A., Tischer M., Furst P., Schafft H., Lahrssen-Wiederholt M. Absorption, distribution, and milk secretion of the perfluoroalkyl acids PFBS, PFHxS, PFOS, and PFOA by dairy cows fed naturally contaminated feed. J. Agric. Food Chem. 2013;61:2903–2912. doi: 10.1021/jf304680j

Lau C, Anitole K, Hodes C, Lai D, Pfahles-Hutchens A, Seed J. 2007. Perfluoroalkyl acids: a review of monitoring and toxicological findings. Toxicol. Sci. 99: 366-394.

Lau C, Thibodeaux JR, Hanson RG, et al. 2003. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. II: Postnatal evaluation. Toxicol Sci 74(2):382-392.

Lau C, Thibodeaux JR, Hanson RG, et al. 2006. Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. Toxicol Sci 90(2):510-518.

Lee SS-T, Pineau T, Drago J, Lee EJ, Owens JW, Kroetz DL, Fernandez-Salguero PM, Westphal H, and Gonzalez FJ. 1995. Targeted disruption of the a isoform of the peroxisome proliferator-activated receptor gene in mice results in abolishment of the pleiotropic effects of peroxisome proliferators. Mol Cell Biol 15:3012–3022

Lee YJ, Kim M-K, Bae J, et al. 2013. Concentrations of perfluoroalkyl compounds in maternal and umbilical cord sera and birth outcomes in Korea. Chemosphere 90(5):1603-1609.

Li K, Gao P, Xiang P, Zhang X, Cui X, Ma LQ. 2017a. Molecular mechanisms of PFOA-induced toxicity in animals and humans: Implications for health risks. 99:43-54.

Li K, Sun J., Yang J, Roberts SM, Zhang X, Cui X, Wei S, Ma LQ. 2017b. Molecular Mechanisms of Perfluorooctanoate-Induced Hepatocyte Apoptosis in Mice Using Proteomic Techniques. Environmental Science & Technology, 51, 11380-11389.

Li Y, Fletcher T, Mucs D, et al. 2018. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occup Environ Med 75(1):46-51. 10.1136/oemed-2017-104651.

Liew Z, et al. 2018. Developmental Exposures to Perfluoroalkyl Substances (PFASs): An Update of Associated Health Outcomes. Current Environmental Health Reports 5:1-19.

Liu J, Li J, Liu Y, et al. 2011. Comparison on gestation and lactation exposure of perfluorinated compounds for newborns. Environ Int 37(7):1206-1212.

Loveless SE, Finlay C, Everds NE, et al. 2006. Comparative responses of rats and mice exposed to linear/branched, linear, or branched ammonium perfluorooctanoate (APFO). Toxicology 220:203-217.

Loveless SE, Hoban D, Sykes G, et al. 2008. Evaluation of the immune system in rats and mice administered linear ammonium perfluorooctanoate. Toxicol Sci 105(1):86-96.

Luebker DJ, Case MT, York RG, et al. 2005a. Two-generation reproduction and cross-foster studies of perfluorooctanesulfonate (PFOS) in rats. Toxicology 215(1-2):126-148.

Luebker DJ, York RG, Hansen KJ, et al. 2005b. Neonatal mortality from in utero exposure to perfluorooctanesulfonate (PFOS) in Sprague-Dawley rats: Dose-response, and biochemical and pharmacokinetic parameters. Toxicology 215(1-2):149-169.

Macon MB, Villanueva LR, Tatum-Gibbs K, et al. 2011. Prenatal perfluorooctanoic acid exposure in CD-1 mice: Low-dose developmental effects and internal dosimetry. Toxicol Sci 122(1):134-145.

Mamsen LS, Björvang RD, Mucs D, Vinnars MT, Papadogiannakis N, Lindh CH, Andersen CY, Damdimopoulou P. 2019. Concentrations of perfluoroalkyl substances (PFASs) in human embryonic and fetal organs from first, second, and third trimester pregnancies. Environ Int. 124:482-492. doi: 10.1016/j.envint.2019.01.010. Epub 2019 Jan 24.

Manzano-Salgado CB, Casas M, Lopez-Espinosa MJ, et al. 2015. Transfer of perfluoroalkyl substances from mother to fetus in a Spanish birth cohort. Environ Res 142:471-478. 10.1016/j.envres.2015.07.020

Michigan Department of Health and Human Services (MIDHHS). 2019. Public health drinking water screening levels for PFAS. Available online at: https://www.michigan.gov/documents/pfasresponse/MDHHS_Public_Health_Drinking_Water_Screening_Levels_for_PFAS_651683_7.pdf

Michigan PFAS Science Advisory Panel Report. 2018. Scientific Evidence and Recommendations for Managing PFAS Contamination in Michigan. December 7, 2018. Available online at: https://www.michigan.gov/documents/pfasresponse/Science_Advisory_Board_Report_641294_7.pdf

Midasch O, Drexler H, Hart N, et al. 2007. Transplacental exposure of neonates to perfluorooctanesulfonate and perfluorooctanoate: A pilot study. Int Arch Occup Environ Health 80:643-648.

Minnesota Department of Health. 2018 - Toxicological Summary for: Perfluorooctanoate: http://www.health.state.mn.us/divs/eh/risk/guidance/gw/pfoa.pdf

Minnesota Department of Health. 2019 - Toxicological Summary for: Perfluorooctane sulfonate: https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfos.pdf

Minnesota Department of Health. 2019 - Toxicological Summary for: Perfluorohexane sulfonate: https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfhxs.pdf

Monroy R, Morrison K, Teo K, et al. 2008. Serum levels of perfluoroalkyl compounds in human maternal and umbilical cord blood samples. Environ Res 108:56-62.

Moriwaki H, et al. 2003. Concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) in vacuum cleaner dust collected in Japanese homes. J. Environ. Monit., 5, 753-757.

Nakayama SF, et al. 2019. Worldwide trends in tracing poly- and perfluoroalkyl substances (PFAS) in the environment. Trends in Analytical Chemistry. Article in press, available online 2/14/19.

Nascimento RA, Nunoo DBO, Bizkarguenaga E, Schultes L, Zabaleta I, Benskin JP, Spanó S, Leonel J. 2018. Sulfluramid use in Brazilian agriculture: A source of per- and polyfluoroalkyl substances (PFASs) to the environment. Environ Pollut. 242(Pt B):1436-1443. doi: 10.1016/j.envpol.2018.07.122.

Needham LL, Grandjean P, Heinzow B, et al. 2011. Partition of environmental chemicals between maternal and fetal blood and tissues. Environ Sci Technol 45(3):1121-1126.

Negri E, et al. 2017. Exposure to PFOA and PFOS and fetal growth: a critical merging of toxicological and epidemiological data. Critical Reviews in Toxicology 47: 482-508.

New Hampshire Department of Environmental Services (NHDES). 2019. Summary Report on the New Hampshire Department of Environmental Services Development of Maximum Contaminant Levels and Ambient Groundwater Quality Standards for Perfluorooctanesulfonic Acid (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorononanoic Acid (PFNA), And Perfluorohexanesulfonic Acid (PFHxS). Available at: https://www.des.nh.gov/organization/commissioner/pip/publications/documents/r-wd-19-01.pdf

Nian M, Li QQ, Bloom M, Qian ZM, Syberg KM, Vaughn MG, Wang SQ, Wei Q, Zeeshan M, Gurram N, Chu C, Wang J, Tian YP, Hu LW, Liu KK, Yang BY, Liu RQ, Feng D, Zeng XW, Dong GH. 2019. Liver function biomarkers disorder is associated with exposure to perfluoroalkyl acids in adults: Isomers of C8 Health Project in China. Environ Res. 172:81-88. doi: 10.1016/j.envres.2019.02.013.

NJ DWQI 2017: NJ Drinking Water Quality Institute (DWQI). 2016. Health-Based Maximum Contaminant Level Support Document: Perfluorooctanoic Acid (PFOA). Available online at: https://www.state.nj.us/dep/watersupply/pdf/pfoa-appendixa.pdf

NJ DWQI 2018: NJ Drinking Water Quality Institute (DWQI). 2018. Health-Based Maximum Contaminant Level Support Document: Perfluorononanoic Acid (PFNA). Available online at: https://www.state.nj.us/dep/watersupply/pdf/pfna-health-effects.pdf

NJ DWQI 2018: NJ Drinking Water Quality Institute (DWQI). 2018. Health-Based Maximum Contaminant Level Support Document: Perfluorooctane Sulfonate (PFOS). Available online at: https://www.state.nj.us/dep/watersupply/pdf/pfos-recommendation-appendix-a.pdf

New York Department of Health (NYDOH), 2018 presentation and professional communications. Presentation available at: https://www.health.ny.gov/environmental/water/drinking/dwqc/

NTP 2016: National Toxicology Program. NTP Monograph: Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid or Perfluorooctane Sulfonate. September 2016.

Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, Zobel LR. 2007. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect 115(9):1298–1305, PMID: 17805419, 10.1289/ehp.10009.

Onishchenko N, Fischer C, Wan Ibrahim WN, et al. 2011. Prenatal exposure to PFOS or PFOA altersmotor function in mice in a sex-related manner. Neurotox Res 19(3):452-461.

Perkins RG, Butenhoff JL, Kennedy GL, et al. 2004. 13-Week dietary toxicity study of ammonium perfluorooctanoate (APFO) in male rats. Drug Chem Toxicol 27(4):361-378.

Porpora MG, Lucchini R, Abballe A, et al. 2013. Placental transfer of persistent organic pollutants: A preliminary study on mother-newborn pairs. Int J Environ Res Public Health 10(2):699-711.

Post GB, Gleason JA, Cooper KR. 2017. Key scientific issues in developing drinking water guidelines for perfluoroalkyl acids: Contaminants of emerging concern. PLoS Biol. 15(12):e2002855. doi: 10.1371/journal.pbio.2002855.

Quist EM, Filgo AJ, Cummings CA, et al. 2015a. Hepatic mitochondrial alteration in CD-1 mice associated with prenatal exposures to low doses of perfluorooctanoic acid (PFOA). Toxicol Pathol 43(4):546-557. 10.1177/0192623314551841.

Quist EM, Filgo AJ, Cummings CA, et al. 2015b. Supplemental data: Hepatic mitochondrial alteration in CD-1 mice associated with prenatal exposures to low doses of perfluorooctanoic acid (PFOA). (Toxicol Pathol 43(4):546-557). Toxicol Pathol 43:546-557.

Ramhoj L, et al. 2018. Perfluorohexane Sulfonate (PFHxS) and a Mixture of Endocrine Disrupters Reduce Thyroxine Levels and Cause Antiandrogenic Effects in Rats. Toxicological Sciences, 163(2), 579-591.

Rappazzo KM, et al. 2017. Exposure to Perfluorinated Alkyl Substances and Health Outcomes in Children: A Systematic Review of the Epidemiologic Literature. International Journal of Environmental Research and Public Health, 14, 691.

Rebholz SL, Jones T, Herrick RL, et al. 2016. Hypercholesterolemia with consumption of PFOA-laced Western diets is dependent on strain and sex of mice. Toxicology reports 3:46-54. 10.1016/j.toxrep.2015.11.004.

Rogers JM, Ellis-Hutchings RG, Grey BE, et al. 2014. Elevated blood pressure in offspring of rats exposed to diverse chemicals during pregnancy. Toxicol Sci 137(2):436-446. 10.1093/toxsci/kft248.

Rosen MB, Abbott BD, Wolf DC, et al. 2008a. Gene profiling in the livers of wild-type and PPARα-null mice exposed to perfluorooctanoic acid. Toxicol Pathol 36(4):592-607.

Rosen MB, Das KP, Rooney J, et al. 2017. PPARα-independent transcriptional targets of perfluoroalkyl acids revealed by transcript profiling. Toxicology Toxicology. 15;387:95-107. doi: 10.1016/j.tox.2017.05.013.

Rosen MB, Lee JS, Ren H, et al. 2008b. Toxicogenomic dissection of the perfluorooctanoic acid transcript profile in mouse liver: Evidence for the involvement of nuclear receptors PPARα and CAR. Toxicol Sci 103(1):46-56.

Rosen MB, Thibodeaux JR, Wood CR, et al. 2007. Gene expression profiling in the lung and liver of PFOA-exposed mouse fetuses. Toxicology 239:15-33.

Schaider LA, et al. 2017. Fluorinated Compounds in U.S. Fast Food Packaging. Environmental Science & Technology Letters, 4, 105-111.

Scher DP, Kelly JE, Huset CA, Barry KM, Hoffbeck RW, Yingling VL, Messing RB. 2018. Occurrence of perfluoroalkyl substances (PFAS) in garden produce at homes with a history of PFAS-contaminated drinking water. Chemosphere. 196:548-555. doi: 10.1016/j.chemosphere.2017.12.179.

Son H, Kim S, Shin HI, et al. 2008. Perfluorooctanoic acid-induced hepatic toxicity following 21-day oral exposure in mice. Arch Toxicol 82:239-246.

Stein CR, McGovern KJ, Pajak AM, et al. 2016. Perfluoroalkyl and polyfluoroalkyl substances and indicators of immune function in children aged 12-19 y: National Health and Nutrition Examination Survey. Pediatr Res 79(2):348-357.

Suh KS, et al. 2017. Perfluorooctanoic acid induces oxidative damage and mitochondrial dysfunction in pancreatic β-cells. Mol Med Rep. 15(6): 3871-3878.

Sundström M, Chang SC, Noker PE, et al. 2012. Comparative pharmacokinetics of perfluorohexanesulfonate (PFHxS) in rats, mice, and monkeys. Reprod Toxicol 33(4):441-451.

Tan X, Xie G, Sun X, et al. 2013. High fat diet feeding exaggerates perfluorooctanoic acid-induced liver injury in mice via modulating multiple metabolic pathways. PLoS ONE 8(4):e61409.

Texas Commission on Environmental Quality (TCEQ). 2016. Perfluorocompounds (PFCs). Available online at: https://www.tceq.texas.gov/assets/public/implementation/tox/evaluations/pfcs.pdf

Thibodeaux JR, Hanson RG, Rogers JM, et al. 2003. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. I: Maternal and prenatal evaluations. Toxicol Sci 74(2):369-381.

Thomford PJ. 2001. 4-Week capsule toxicity study with ammonium perfluorooctanoate (APFO) in Cynomolgus monkeys. APME Ad-Hoc APFO toxicology working group.

Thompson J, Lorber M, Toms LM, et al. 2010. Use of simple pharmacokinetic modeling to characterize exposure of Australians to perfluorooctanoic acid and perfluorooctane sulfonic acid. Environ Int 36(4):390-397. 10.1016/j.envint.2010.02.008.

Trudel D, et al. 2008. Estimating Consumer Exposure to PFOS and PFOA. Risk Analysis, 28(2), 251-269. Erratum issued, 2008. Risk Analysis, 28(3), 807.

Trudel D, Horowitz L, Wormuth M, Scheringer M, Cousins IT, Hungerbuheler K. 2008. Estimating consumer exposure to PFOS and PFOA. Risk Anal. 28: 251-269.

Tucker DK, Macon MB, Strynar MJ, et al. 2015. The mammary gland is a sensitive pubertal target in CD-1 and C57Bl/6 mice following perinatal perfluorooctanoic acid (PFOA) exposure. Reprod Toxicol 54:26-36. 10.1016/j.reprotox.2014.12.002.

Tyagi S, Gupta P, Saini AS, Kaushal C, Sharma S (October 2011). "The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases". J Adv Pharm Technol Res. 2(4): 236–40.

USEPA (U.S. Environmental Protection Agency). 2000. Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000) Documents. Accessed online at: https://www.epa.gov/wqc/methodology-deriving-ambient-water-quality-criteria-protection-human-health-2000-documents

USEPA (U.S. Environmental Protection Agency). 2002. A Review of the Reference Dose and Reference Concentration Processes. EPA/630/P-02/0002F. Risk Assessment Forum, Washington, DC. Accessed online at: https://www.epa.gov/osa/review-reference-dose-and-reference-concentration-processes

USEPA (U.S. Environmental Protection Agency). 2011. Exposure Factors Handbook: 2011 Edition. EPA/600/R-090/052F. Office of Research and Development, National Center for Environmental Assessment, Washington, D.C. 1436 pp. Accessed online at: https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252.

USEPA (U.S. Environmental Protection Agency). Benchmark Dose Technical Guidance. Document # EPA/100/R-12/001. June 2012. Accessed online at: https://www.epa.gov/risk/benchmark-dose-technical-guidance

USEPA (U.S. Environmental Protection Agency). 2016a. Health Effects Support Document for Perfluorooctanoic acid (PFOA). Document # EPA 822-R-16-003. May 2016. Accessed online at: https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_hesd_final_508.pdf

USEPA (U.S. Environmental Protection Agency). 2016b. Health Effects Support Document for Perfluorooctane Sulfonate (PFOS). Document # EPA 822-R-16-002. May 2016. Accessed online at: https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf

USEPA (U.S. Environmental Protection Agency). 2019. Exposure Factors Handbook: Chapter 3 Update. EPA/600/R-090/052F. Office of Research and Development, National Center for Environmental Assessment, Washington, D.C. Accessed online at: https://www.epa.gov/sites/production/files/2019-02/documents/efh_-_chapter_3_update.pdf

Vanden Heuvel JP, Thompson JT, Frame SR, et al. 2006. Differential activation of nuclear receptors by perfluorinated fatty acid analogs and natural fatty acids: A comparison of human, mouse, and rat peroxisome proliferator-activated receptor-α, -ß, and -γ, liver x receptor-ß, and retinoid x receptor-α. Toxicol Sci 92(2):476-489.

Vélez MP, Arbuckle TE, Fraser WD. 2015. Maternal exposure to perfluorinated chemicals and reduced fecundity: The MIREC study. Hum Reprod 30(3):701-709. 10.1093/humrep/deu350.

Verner MA, Loccisano AE, Morken NH, et al. 2015. Associations of perfluoroalkyl substances (PFAS) with lower birth weight: An evaluation of potential confounding by glomerular filtration rate using a physiologically based pharmacokinetic model (PBPK). Environ Health Perspect 123(12):1317-1324.

Viberg H, Lee I, Eriksson P. 2013. Adult dose-dependent behavioral and cognitive disturbances after a single neonatal PFHxS dose. Toxicology 304:185-191.

Vieira VM, Hoffman K, Shin M, et al. 2013. Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: A geographic analysis. Environ Health Perspect 121(3):318-323.

Wan HT, Zhao YG, Leung PY, et al. 2014b. Perinatal exposure to perfluorooctane sulfonate affects glucose metabolism in adult offspring. PLoS ONE 9(1):e87137. 10.1371/journal.pone.0087137.

Wang H, Du H, Yang J, Jiang H, O K, Xu L, Liu S, Yi J, Qian X, Chen Y, Jiang Q, He G. 2019. S, PFOA, estrogen homeostasis, and birth size in Chinese infants. Chemosphere. 221:349-355. doi: 10.1016/j.chemosphere.2019.01.061.

Wang J, Yan S, Zhang W, et al. 2015. Integrated proteomic and miRNA transcriptional analysis reveals the hepatotoxicity mechanism of PFNA exposure in mice. J Proteome Res 14(1):330-341. 10.1021/pr500641b.

Washburn ST, et al. 2005. Exposure assessment and risk characterization for perfluorooctanoate in selected consumer articles. Environmental Science & Technology, 39(11), 3904-10.

White SS, Calafat AM, Kuklenyik Z, et al. 2007. Gestational PFOA exposure of mice is associated with altered mammary gland development in dams and female offspring. Toxicol Sci 96(1):133-144.

White SS, Kato K, Jia LT, et al. 2009. Effects of perfluorooctanoic acid on mouse mammary gland development and differentiation resulting from cross-foster and restricted gestational exposures. Reprod Toxicol 27(3-4):289-298.

White SS, Stanko JP, Kato K, et al. 2011. Gestational and chronic low-dose PFOA exposures and mammary gland growth and differentiation in three generations of CD-1 mice. Environ Health Perspect 119(8):1070-1076.

WHO. e-Library of Evidence for Nutrition Actions (eLENA). 2019. Exclusive breastfeeding for optimal growth, development and health of infants. Available online at: https://www.who.int/elena/titles/exclusive_breastfeeding/en/

Winkens K, et al. 2017. Early life exposure to per- and polyfluoroalkyl substances (PFASs): A critical review. Emerging Contaminants, 3, 55-68.

Winkens K, et al. 2018. Perfluoroalkyl acids and their precursors in floor dust of children's bedrooms – Implications for indoor exposure. Environment International, 119, 493-502.

Winkens K, Giovanoulis G, Koponen J, Vestergren R, Berger U, Karvonen AM, Pekkanen J, Kiviranta H, Cousins IT. 2018. Perfluoroalkyl acids and their precursors in floor dust of children's bedrooms - Implications for indoor exposure. Environ Int. 119:493-502. doi: 10.1016/j.envint.2018.06.009.

Wolf CJ, Fenton SE, Schmid JE, et al. 2007. Developmental toxicity of perfluorooctanoic acid in the CD-1 mouse after cross-foster and restricted gestational exposures. Toxicol Sci 95(2):462-473.

Wolf CJ, Schmid JE, Lau C, et al. 2012. Activation of mouse and human peroxisome proliferator-activated receptor-alpha (PPARa) by perfluoroalkyl acids (PFAAs): Further investigation of C4-C12 compounds. Reprod Toxicol 33:546-551.

Wolf CJ, Takacs ML, Schmid JE, et al. 2008. Activation of mouse and human peroxisome proliferator-activated receptor alpha by perfluoroalkyl acids of different functional groups and chain lengths. Toxicol Sci 106(1):162-171.

Wolf CJ, Zehr RD, Schmid JE, et al. 2010. Developmental effects of perfluorononanoic Acid in themouse are dependent on peroxisome proliferator-activated receptor-alpha. PPAR Res 2010 10.1155/2010/282896.

Worley RR, Yang X, Fisher J. 2017. Physiologically based pharmacokinetic modeling of human exposure to perfluorooctanoic acid suggests historical non drinking-water exposures are important for predicting current serum concentrations. Toxicol Appl Pharmacol. 330:9-21. doi: 10.1016/j.taap.2017.07.001.

Yahia D, El-Nasser MA, Abedel-Latif M, et al. 2010. Effects of perfluorooctanoic acid (PFOA) exposure to pregnant mice on reproduction. J Toxicol Sci 35(4):527-533.

Yahia D, Tsukuba C, Yoshida M, et al. 2008. Neonatal death of mice treated with perfluorooctane sulfonate. J Toxicol Sci 33(2):219-226.

Yang L, Wang Z, Shi Y, et al. 2016. Human placental transfer of perfluoroalkyl acid precursors: Levels and profiles in paired maternal and cord serum. Chemosphere 144:1631-1638. 10.1016/j.chemosphere.2015.10.063.

Zeng HC, Li YY, Zhang L, et al. 2011. Prenatal exposure to perfluorooctanesulfonate in rat resulted in long-lasting changes of expression of synapsins and synaptophysin. Synapse 65(3): 225-33.

Zeng XW, Bloom MS, Dharmage SC, Lodge CJ, Chen D, Li S, Guo Y, Roponen M, Jalava P, Hirvonen MR, Ma H, Hao YT, Chen W, Yang M, Chu C, Li QQ, Hu LW, Liu KK, Yang BY, Liu S, Fu C, Dong GH. 2019. Prenatal exposure to perfluoroalkyl substances is associated with lower hand, foot and mouth disease viruses antibody response in infancy: Findings from the Guangzhou Birth Cohort Study. Sci Total Environ. 663:60-67. doi: 10.1016/j.scitotenv.2019.01.325.

Zhang T, Sun H, Lin Y, Qin X, Zhang Y, Geng X, Kannan K. 2013. Distribution of poly- and perfluoroalkyl substances in matched samples from pregnant women and carbon chain length related maternal transfer. Environ Sci Technol. 47(14):7974-81. doi: 10.1021/es400937y.

Zhang Y, Beesoon S, Zhu L, et al. 2013. Biomonitoring of perfluoroalkyl acids in human urine and estimates of biological half-life. Environ Sci Technol 47(18):10619-10627. 10.1021/es401905e.

Zhu Y, Qin XD, Zeng XW, et al. 2016. Associations of serum perfluoroalkyl acid levels with T-helper cell-specific cytokines in children: By gender and asthma status. Sci Total Environ 559:166-173. 10.1016/j.scitotenv.2016.03.187.

June 25, 2019

Clark Freise
Assistant Commissioner
New Hampshire Department of Environmental Services
29 Hazen Drive
Concord, NH 03302

Dear Mr. Freise:

I have reviewed at your request the *New Hampshire Department of Environmental Services Technical Background for the June 2019 Proposed Maximum Contaminant Levels (MCLs) for Perfluorooctanoate (PFOA), Perfluorooctane sulfonate (PFOS), Perfluorononanoate (PFNA) and Perfluorohexane Sulfonate (PFHxS).* This document was prepared by Jonathan Ali, Ph.D., Mary Butow, M.S., and David Gordon, M.S., of the Permitting & Environmental Health Bureau and is dated June 7, 2019. This document updates drinking water standards for PFOA, PFOS, PFNA, and PFHxS originally proposed by the Department on December 31, 2018, taking into consideration recently published studies, as well as public comments on the original proposed Maximum Contaminant Levels (MCLs). Because the updated analysis is intended to be responsive to public comments, I have also read the public comments on the original proposed MCLs as part of my review.

All of the proposed MCLs are risk-based, meaning that the numerical value of the MCL is determined solely by what is determined to be a safe dose limit for the chemical in drinking water. Typically, risk-based criteria (i.e., concentration limits) for drinking water are derived using rather simplistic equations that combine some expression of the safe dose of the chemical with assumptions regarding drinking water consumption rate. The drinking water consumption rate is usually derived from an upper percentile value for a segment of the population [often, all adults]. Poly- and perfluoroalkyl substances (PFAS) are among the few environmental contaminants for which significant data are available regarding blood concentrations associated with adverse health effects, both in humans and animal models used in toxicity studies. This information, combined with information on the toxicokinetics of PFAS in humans and animals, allows safe levels of exposure to be based on blood concentrations and drinking water consumption that would produce those blood concentrations. Although this requires a more complex analysis than traditional methods for deriving MCLs, it provides a more rigorous and scientifically defensible basis for extrapolating dose-response relationships for toxicity observed in animals to humans.

The New Hampshire Department of Environmental Services (NHDES) and others have taken this approach for development of risk-based standards for PFAS in drinking water, but NHDES has taken it a step further. There is concern for PFAS exposure in infants, not only because some PFAS have been shown to produce adverse developmental effects in animals, but also because infants may have the highest blood concentrations of any life stage due to their small body weight and intake from

breastmilk or from formula made from PFAS contaminated water. This means that infants may be more susceptible to not only developmental effects from PFAS, but to other PFAS effects as well. To address explicitly potential risks from early life exposure to the four PFAS for which MCLs are proposed, NHDES has used a model recently developed by the Minnesota Department of Health (Goeden et al. 2019) that predicts blood concentrations of PFAS beginning at birth and extending into adulthood. The predicted blood concentrations of PFOA, PFOS, PFNA, and PFHxS using this model show clearly the importance of considering early life drinking water exposures, both direct and indirect, and allow demonstration that the proposed MCLs are protective at all life stages. This is a significant advance over the previous derivation of PFAS MCLs by the Department, and over most of the drinking water standards for PFAS developed elsewhere.

A critical aspect of the calculation of risk-based MCLs for PFAS is the derivation of safe dose limits, or reference doses. Development of these reference doses requires identification of a critical effect and study that provides dose-response information for that effect, determining a no-effect level from the data, selection of uncertainty factors to insure a health protective value in the face of limitations in the available data, and identifying a human equivalent dose based upon the toxicokinetics of the chemical in humans. The proposed MCLs in the June 2019 document include refinements in the reference doses for PFOA, PFOS, PFNA, and PFHxS presented in the January 2019 report based on consideration of new information, new analyses, and public comments. These include a change in critical effect (PFOS), total uncertainty factor (PFNA), modeling of toxicity data (PFHxS), and Dosimetric Adjustment Factor (PFOA, PFNA, PFHxS) to estimate a human equivalent oral dose. The rationale for each of the changes is clearly articulated in the report and all are well justified scientifically, in my opinion. I should note that a colleague, Dr. Leah Stuchal, and I collaborated with Dr. Ali of NHDES on the dose-response analysis for PFHxS presented in this report.

A number of public commenters took issue with one or more of the uncertainty factors selected for the derivation of initial reference doses for PFOA, PFOS, PFNA, and PFHxS in the January 2019 document. The selection of uncertainty factors for these and other chemicals is undoubtedly important as they have a direct impact on the risk-based drinking water standards that are derived. I have served as a peer reviewer for the U.S. EPA for many years on topics including proposed reference doses for several chemicals, primary through service on the Chartered Science Advisory Board and the Chemical Assessment Advisory Committee. Selection of uncertainty factors involves a good deal of scientific judgment, and despite guidance from the U.S. EPA on how uncertainty factor values should be selected in a given situation, it is often difficult to get complete agreement among objective scientists. So the number, and sometimes contradictory nature, of suggestions among public commenters regarding choices of uncertainty factors is not surprising. As with other aspects of reference dose development, I found the rationale for selection of uncertainty factors presented in the current document to be clear and consistent with U.S. EPA guidance. The comparison in Table 2 of uncertainty factors selected by NHDES with those chosen by other agencies that have developed reference doses for these chemicals shows that they are in line with judgments made by other regulatory scientists.

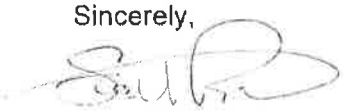
Another issue raised by public commenters is the overall level of conservatism inherent in the originally proposed MCL values, with comments offered in both directions — too conservative or not conservative enough. Concern that the initial MCLs were not

sufficiently conservative in that they were not clearly protective of infants has been addressed by NHDES through use of modeling that includes breastfed and formula-fed infants. For other, more general aspects of MCL derivation, NHDES is reasonably transparent in its attempts to strike the right balance of conservatism — conservative enough to provide confidence that the proposed MCLs are health protective without excessive conservatism that undermines the credibility of the results. Conservative choices are identified as such, and are used in combination with central tendency values for other inputs in an effort to create upper end, but not unrealistic estimates of risk. In my opinion, the level of conservatism achieved is entirely consistent with current risk assessment practice by state and federal environmental agencies.

As noted in the report, study of the potential health impacts of PFAS exposure is a rapidly changing field, and new information is becoming available almost continuously. Nevertheless, environmental regulatory agencies must often capture existing science as best they can and move forward with environmental criteria. Overall, I found the derivation of the MCLs proposed in the Technical Background document to be clearly described and scientifically sound, taking advantage of the most recent data and technical approaches.

The opinions expressed in this review are solely my own and do not necessarily reflect those of my employer, the University of Florida.

Sincerely,



Stephen M. Roberts, Ph.D.

Reference cited:

Goeden; HM, Greene CW, Jacobus JA. A transgenerational toxicokinetic model and its use in derivation of Minnesota PFOA water guidance. J. Expos. Sci. Environ. Epi. 29:183-195, 2019.

ATTACHMENT 2

New Hampshire Department of Environmental Services

Update on Cost and Benefit Consideration

June 28, 2019

NEW HAMPSHIRE DEPARTMENT OF ENVIRONMENTAL SERVICES

UPDATE ON CONSIDERATION OF THE COSTS AND BENEFITS RELATED TO FINAL PROPOSED MAXIMUM CONTAMINANT LEVELS AND AMBIENT GROUNWATER QUALITY STANDARDS FOR PERFLUOROOCTANESULFONIC ACID (PFOS), PERFLUOROOCTANOIC ACID (PFOA), PERFLUORONONANOIC ACID (PFNA), AND PERFLUOROHEXANESULFONIC ACID (PFHXS)

6/28/2019

Chapter Law RSA 345 requires the New Hampshire Department of Environmental Services to consider what is known about cost and benefit to affected parties when proposing maximum contaminant levels (MCLs) and ambient groundwater quality standards (AGQSs). This consideration was documented in the "Summary Report on the New Hampshire Department of Environmental Services Development of Maximum Contaminant Levels and Ambient Groundwater Quality Standards for Perfluorooctanesulfonic Acid (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorononanoic Acid (PFNA), and Perfluorohexanesulfonic Acid (PFHxS)", dated January 4, 2019 (January 2019 report), for the initial proposed rules and is updated here for the final proposal. As was the case for the initial proposal, the emerging nature of PFAS contamination limits the availability of certain information that would be needed for a complete quantification of all the costs and benefits that will result from adopting these rules. Examples of these limitations include not having extensive sampling data for all potential contamination sources and public water systems statewide and having an incomplete understanding of all the health impacts associated with exposure to these four PFAS. Since the initial proposal, NHDES has continued to gather information and further research what is known about costs and benefits to consider in determining the standards to be included in the final proposal. Consideration of the updated information was performed and due to the clear, although difficult to quantify, health benefits in limiting exposure, the department chose to not alter the health based standards, despite recognizing the significant implementation costs.

Additional information on costs and benefits considered is provided below:

BENEFITS:

In the case of benefits, a number of new studies continue to suggest significant health impacts related to these four compounds, confirming that PFAS may:

- Increase cholesterol levels
- Increase liver enzyme levels
- Affect growth, learning, and behavior
- Interfere with the body's natural hormones, including thyroid hormone levels and sex hormone levels that could affect reproductive development and a woman's fertility
- Affect the immune system (e.g., decrease how well the body responds to vaccines)
- Increase the risk of certain types of cancers

These same health risks are identified by the Agency for Toxic Substances and Disease Registry (ATSDR) an agency within the Centers for Disease Control (CDC). https://www.atsdr.cdc.gov/pfas/health-effects.html

Additionally, the recent publication "A transgenerational toxicokinetic model and its use in derivation of Minnesota PFOA water guidance" provides a peer reviewed method to estimate blood serum levels that result from exposure to PFOA (later papers and one currently under peer review documented similar capabilities for PFOS, PFNA and PFHxS) in infants and children. As the statute specifically required that proposed standards provide "*an adequate margin of safety to protect human health at all life stages, including but not limited to pre-natal development*", this insight into how developmental-stage blood serum levels respond to different amounts of each of the four PFAS in drinking water strongly suggests that the proposed lower MCLs/AGQSs are necessary to keep infant and children blood serum levels below the levels that indicate enhanced risk of the various health endpoints identified by the ATSDR above.

As was described in the January 2019 report, NHDES was not able to monetize the avoided health impact costs. However, some of these impacts are clearly associated with the developmental stage of life and therefore can have significant through-life costs such as direct health care treatment costs, the associated losses of economic production and income of those impacted, and the associated impacts to families and caregivers. NHDES came to this conclusion after reviewing the most recent published research and speaking with experts, including a group of professors and researchers at the University of New Hampshire (UNH) with whom NHDES recently contracted to quantify the benefits of reducing the arsenic MCL. After filing the initial proposal, NHDES continued to reach out to experts and search for valid methods for quantifying benefit. Two recent studies were identified that have attempted to quantify benefits. The utility of both these studies is discussed below. The lack of science identifying direct causality between health impacts and these compounds continues to limit quantification of benefit, as was discussed in the January 2019 report related to utilizing contingent valuation studies. It should be noted that this is not unique to PFAS regulation in other states, other compounds have been regulated once the linkage to negative health impacts was documented, but before direct causality and dose/rate relationships were clearly known. This precautionary process is followed in drinking water regulation to limit the harm identified while the exact benefit is quantified through longer term studies. NHDES, based on the most recent studies, is confident that there is a clear and significant benefit to reducing exposure to these compounds through drinking water while additional studies will help to more accurately quantify the specific health care costs avoided from the known, and to be discovered, specific health impacts caused by these four PFAS compounds.

A new study produced by the Nordic Council of Ministers "The Cost of Inaction, A socioeconomic analysis of environmental and health impacts linked to exposure to PFAS" has attempted to quantify costs associated with low, medium and high risks of exposure to PFAS. This report assumes that PFAS as a group directly causes certain associated health impacts and then assumes a percentage of reported health events, for instance for kidney cancer, is caused by exposure to PFAS above certain levels. While not directly of utility to quantifying the health benefit associated with the proposed standards for these four compounds in New Hampshire, it does provide further estimation of the avoided costs that could be associated with reduced exposure to PFAS. A summary of the report is attached.

Similarly, a recent study used a previous study, that showed a clear link between low to moderate exposure to PFOA and reduced birth weights, to estimate health impact costs. This study, "Perfluorooctanoic acid and low birth weight: Estimates of US attributable burden and economic costs from 2003 through 2014", showed that while blood serum levels in the general US population are going down, there are still impacts to birth weights and attempted to quantify the through-life cost impacts of

those reduced birth weights. This is based on the National Health and Nutrition Examination Survey (NHANES) database where the general population is measured on a number of factors, including PFAS blood serum levels. It is important to note that a number of New Hampshire communities have measured blood serum levels significantly above those found in the NHANES data, which implies there is significant benefit in reducing exposures to better align with the national averages, as this study indicates there are still health impacts (reduced birth weight) that could be reduced by limiting exposure prior to and during pregnancy. While this study cannot be directly related to NH's population to quantify a benefit due to health cost mitigation, it did calculate (for the entire United States population) that the health impacts due to reduced birth weight were $347 million in 2013-2014. It is a consideration that the national averages for PFOA blood serum levels during this time period were half what has been measured recently in some impacted NH communities. The cost implications estimated in the study when the US population had similar blood serum levels to NH's impacted communities was approximately $2.7B. While this does not quantify the benefits of reduced PFAS exposure, it does imply that the benefits are significant.

Finally, the treatment that will be used at most public water systems that exceed an MCL(s) is granular activated carbon. This treatment may provide an ancillary benefit of removing many other substances such as any new emerging chemicals and other unregulated, not well studied PFAS.

COSTS

Where data was available to derive estimates of implementation costs, the information including all assumptions was provided in the January 4, 2019, report. These estimates have been updated based on the newly proposed standards (i.e. costs to public water systems, groundwater discharge permittees and landfill and hazardous waste site ground water management permittees). Public comments were broadly received commenting on the methods used by NHDES and providing recent quotes for treatment systems in design or implementation. Some of these updated costs validated the methods used by NHDES and none of the comments identified any systemic flaws in the approach used. Therefore, NHDES has chosen to continue to use the original assumptions which provide uniformity across source types and allow direct comparison of the costs resulting from the lowered standards. The following table provides the summary of the initial cost estimates and the new estimated costs.

PFAS Source Type	Initial Proposal Estimate	Final Proposal Estimate
Public Water Systems*	Initial Treatment Costs: $1,851,354 - $5,171,022 Initial Sampling: $1,102,500 - $2,836,000 Annual O&M Costs: $114,912 - $223,439 Annual Sampling Costs $73,055 - $184,825	Initial Treatment Costs: $65,046,987 - $142,822,884 Initial Sampling: $1,102,500 - $2,836,000 Annual O&M Costs: $6,914,552 - $13,444,963 Annual Sampling Costs $174,257 - $444,409
Active Hazardous Waste Sites*	Initial Corrective Action Costs:	Initial Corrective Action Costs:

	$1,350,000 _ $2,310,000 Annual Operating Costs: $570,000 - $1,020,000	$2,315,000 - $4,440,000 Annual Operating Costs: $980,000 - $1,795,000
Municipal Landfills*	Initial Corrective Action Costs: $380,000 – 755,000 Annual Operating Costs: $260,000 - $390,000	Initial Corrective Action Costs: $935,000 - $1,755,000 Annual Operating Costs: $465,000 - $770,000
Wastewater Discharges to Groundwater*	Initial Corrective Action Costs: $1,100,000 Annual Operating Costs: $200,000 - $400,000	Initial Corrective Action Costs: $5,000,000 Annual Operating Costs: $ 849,000 - $1,600,000

* Assumptions for public water systems are contained in the January 9, 2019, report and include treatment of sources that exceed the MCL verses taking the well off line, blending or inter-connecting. For all other costs categories, see attached tables that provide assumptions and calculations used to create these estimates.

Adopting MCLs and AGQSs does not require private well owners to test for or treat their water supplies. However, given the publicity concerning these contaminants and the low standards for them in public drinking water, it is likely that many homeowners may voluntarily choose to test and install treatment in their homes. Based on sampling in areas without likely sources of PFAS contamination, NHDES estimates that as much as 9% of the estimated 250,000 private wells will exceed the proposed standards which could result in an estimated initial cost of treatment of $70,895,522 and annual maintenance cost of $21,268,657. This is likely an overestimation since some homeowners will choose not to test, and some who test will choose not to treat.

In general, the qualitative explanation for sites that may be potential sources of contamination for which we have no or very limited data remains the same as what was presented in the January report. An exception to this is municipal fire stations. Based on an ongoing initiative to test 34 fire stations that may have used AFFF foams and are located in close proximity to wells, only 2 have levels above the proposed standards to date. This suggests there may be limited occurrence of PFAS at levels above the proposed standards near fire stations and accordingly costs associated with this potential source type may be overestimated in the January 9, 2019 report.

Table 1. Estimated Cost To Hazardous Waste and Landfill Sites for Proposed PFAS MCLs

Est. No. Hazardous Waste Sites	Est. No. of Landfill Sites	Additional Capital Costs	Hazardous Waste Sites	Landfill Sites	Additional Annual Costs	Hazardous Waste Sites	Landfill Sites
Projected # of existing Sites w/ PFAS Exceedances		***GMP Expansion of Existing Sites***	***Est. Cost***	***Est. Cost***	***GMP Expansion of Existing Sites***	***Est. Cost***	***Est. Cost***
		A Monitoring Network Enhancments			**A Annual Sampling and Reporting**		
252	84	Monitoring Well Install (assume 3 wells) + Initial Sampling Round	$ 12,000	$ 12,000	Annual Sampling/Lab fee (1 round, 3 wells)	$ 3,000	$ 3,000
		Receptor Survey	$ 1,000	$ 1,000	Annual GMP Reporting	$ 2,400	$ 2,400
		Est. Subtotal Capital Cost	$ 13,000	$ 13,000	Est. Subtotal Annual Cost	$ 5,400	$ 5,400
		Numbers below rounded to the nearest $5,000			Numbers below rounded to the nearest $5,000		
		Est. Total Capital Costs for GMP Expansion (assumes 35% of all sites require expansion)	**$ 1,145,000**	**$ 385,000**	***Est. Total Annual Monitoring/Reporting Costs (assumes 35% of all sites require expansion)***	**$ 475,000**	**$ 160,000**
		Est. Total Capital Cost for GMP Expansion (assumes 75% of all sites require expansion)	**$ 2,455,000**	**$ 820,000**	***Est. Total Annual Monitoring/Reporting Costs (assumes 60% of all sites require expansion)***	**$ 1,020,000**	**$ 340,000**
		B Water Supply Well Treatment			**B Water Supply Well Treatment**		
		POE Install -assume 3 per site	$ 3,000	$ 3,000	Annual O&M of POE (assume 3 per site)	$ 1,000	$ 1,000
		Est. Subtotal Cost	$ 9,000	$ 9,000	Est. Subtotal Annual O&M Cost	$ 3,000	$ 3,000
		Numbers below rounded to the nearest $5,000			Numbers below rounded to the nearest $5,000		
		Est. Total for Expansion of Sites 15% of all sites will have 3 new POEs	**$ 340,000**	**$ 115,000**	***Est. Total for Expansion of Sites 15% of all sites will have 3 new POEs***	**$ 115,000**	**$ 40,000**
		Est. Total for Expansion of Sites - 25% of all sites will have 3 new POEs	**$ 565,000**	**$ 190,000**	***Est. Total for Expansion of Sites 25% of all sites will have 3 new POEs***	**$ 190,000**	**$ 65,000**
					C NHDES Staff Time (Assume Annual Salary/benefits for 2 FTE staff will be required at $120/yr)	$ 120,000	$ 120,000
		I. Est. Capital Cost range for GMZ Expansion: Low	**$ 1,485,000**	**$ 500,000**	**I. Est. Annual Cost range for GMZ Expansion: Low**	**$ 710,000**	**$ 320,000**
		High	**$ 3,020,000**	**$ 1,010,000**	**High**	**$ 1,330,000**	**$ 525,000**
Projected # of Sites w/ PFAS Exceedances as new Contaminant of Concern		***Sites that may be required to address PFAS as a new Contaminant of Concern***	***Est. Cost***	***Est. Cost***	***Sites that may be required to address PFAS as a new Contaminant of Concern***	***Est. Cost***	***Est. Cost***
		A Monitoring Network Enhancments			**A Annual Sampling and Reporting**		
101	53	Monitoring Well Install (assume 5 wells) + Initial Sampling Round	$ 18,000	$ 18,000	Annual Sampling/Lab fee (1 round, 5 wells)	$ 3,500	$ 3,500
		Receptor Survey	$ 1,500	$ 1,500	Annual GMP Reporting	$ 2,900	$ 2,900
		Est. Subtotal Cost	$ 19,500	$ 19,500	Est. Subtotal Cost	$ 6,400	$ 6,400
		Numbers below rounded to the nearest $5,000			Numbers below rounded to the nearest $5,000		
		Est. Total for New Sites - 35%	**$ 695,000**	**$ 365,000**	***Est. Total Annual Monitoring Costs for New Sites - 35% of all sites***	**$ 225,000**	**$ 120,000**
		Est. Total for New Sites - 60%	**$ 1,190,000**	**$ 625,000**	***Est. Total Annual Monitoring Costs for New Sites - 60% of all sites***	**$ 390,000**	**$ 205,000**
		B Water Supply Well Treatment			**B Water Supply Well Treatment**		
		POE Install - assume 3 per site	$ 3,000	$ 3,000	Annual O&M of POE (assume 3 per site)	$ 1,000	$ 1,000
		Est. Subtotal Cost	$ 9,000	$ 9,000	Est. Subtotal Cost	$ 3,000	$ 3,000
		Numbers below rounded to the nearest $5,000			Numbers below rounded to the nearest $5,000		
		Est. Total for New Sites 15% of all sites will have 3 new POEs	**$ 135,000**	**$ 70,000**	***Est. Total for New Sites 15% of all sites will have 3 new POEs***	**$ 45,000**	**$ 25,000**
		Est. Total for New Sites 25% of all sites will have 3 new POEs	**$ 230,000**	**$ 120,000**	***Est. Total for New Sites 25% of all sites will have 3 new POEs***	**$ 75,000**	**$ 40,000**
		II. Est. Cost range for Sites w/ PFAS as New COC: Low	**$ 830,000**	**$ 435,000**	**I. Est. Annual Cost range for Sites w/ PFAS as New COC: Low**	**$ 270,000**	**$ 145,000**
		High	**$ 1,420,000**	**$ 745,000**	**High**	**$ 465,000**	**$ 245,000**
		Est. Total Capital Cost Impacts for Proposed MCLs: Low	**$ 2,315,000**	**$ 935,000**	**Est. Total Annual Operating Budget Impacts for Proposed MCLs: Low**	**$ 980,000**	**$ 465,000**
		High	**$ 4,440,000**	**$ 1,755,000**	**High**	**$ 1,795,000**	**$ 770,000**

Hazardous Waste Sites	Landfills	
$2.32M to $4.44M	$935K to $1.80M	Additional capital cost to expand existing GMZs, establish new sites and treat impacted drinking water supply wells
$935K to $1.76M	$465K to $770K	Additional annual operating costs (monitoring and reporting), and NHDES permit administration costs

For the Following Standards (ng/L):
PFOA = 12
PFOS = 15
PFNA = 11
PFHxS = 18

Updated: 5/7/2019

Table 1. Estimated Cost To Hazardous Waste and Landfill Sites for Proposed PFAS MCLs

Hazardous Waste Site Projections are based on:	
515	Hazardous Waste Sites
137	Number of sites PFAS Sampling has been completed
27%	Percent of Sites Sampled
Analysis of Existing Data and Current Standard of 70 PPT PFOA + PFOS	
Of the 137 sites sampled:	
49%	had exceedances of the current standard
9%	had water supply wells with exceedances of current standards
Estimate of # of Hazardous Waste Sites with Existing PFAS Compliance Issues	
Assumption: *Apply similar trend of existing data outlined above.*	
252	sites may have exceedances of the current standard
25 to 50	estimated number of sites with drinking water impacts[1]
Analysis of Existing Data and Proposed Standards in Parts per Trillion	
PFOA	12
PFOS	15
PFNA	11
PFHxS	18
69%	of sites sampled w/ exceed. of proposed stds of one or more compounds
53 to 88	estimated number of sites with drinking water impacts[1]

Notes:
1. Based on the limited data to estimate this, NHDES used a range of 15-25% of the projected number of sites with exceedances.

Landfill Site Projections are based on:	
201	Landfill Sites
117	Number of sites PFAS Sampling has been completed
58%	Percent of Sites Sampled
Analysis of Existing Data and Current Standard of 70 PPT PFOA + PFOS	
Of the 117 sites sampled:	
42%	had exceedances of the current standard
1%	had water supply wells with exceedances of current standards
Estimate of # of Landfill Sites with Existing PFAS Compliance Issues	
Assumption: *Apply similar trend of existing data outlined above.*	
84	sites may have exceedances of the current standard
8 to 17	estimated number of sites with drinking water impacts[1]
Analysis of Existing Data and Proposed Standards in Parts per Trillion	
PFOA	12
PFOS	15
PFNA	11
PFHxS	18
68%	sites sampled w/ exceed. of proposed stds of one or more compounds
21 to 34	estimated number of sites with drinking water impacts[1]

Notes:
1. Based on the limited data to estimate this, NHDES used a range of 15-25% of the projected number of sites with exceedances.

Updated: 5/7/2019

Cost Estimates - Reduction in PFAS Standards - Groundwater Discharge Permit Sites

Isolated Sites : Non-Developed Areas, Able to Expand GDZ, No Private/Public Water Supply Receptors

Small GWDP Sites
Non POTW sites, usually privately owned

Additional Capital Costs

Item	Count	Unit Cost	Total
Mon Well	3	$ 12,000	$ 36,000
Priv Well Svy	1	$ 1,000	$ 1,000
		Total	*$ 37,000*
5X	*Add'l sites*		*$ 185,000*

Additional Annual Costs

Item	Count	Unit Cost	Total
Smpl Rnd	6	$ 1,000	$ 6,000
Rpting	1	$ 2,400	$ 2,400
		Total	*$ 8,400*
5X	*Add'l sites*		*$ 42,000*

Large GWDP Sites
POTW sites, usually publicly owned

Additional Capital Costs

Item	Count	Unit Cost	Total
Mon Well	6	$ 12,000	$ 72,000
Priv Well Svy	1	$ 1,000	$ 1,000
		Total	*$ 73,000*
18X	*Add'l sites*		*$ 1,314,000*

Additional Annual Costs

Item	Count	Unit Cost	Total
Smpl Rnd	12	$ 1,000	$ 12,000
Rpting	1	$ 2,400	$ 2,400
		Total	*$ 14,400*
18X	*Add'l sites*		*$ 259,200*

Non-Isolated Sites : Developed Areas, Not (Easily) Able to Expand GDZ, Private/Public Water Supply Receptors Present

Small GWDP Sites
Non POTW sites, usually privately owned

Additional Capital Costs

Item	Count	Unit Cost	Total
Mon Well	2	$ 12,000	$ 24,000
Priv Well Svy	1	$ 2,500	$ 2,500
POE-PFAS	3	$ 3,000	$ 9,000
		Total	*$ 35,500*
Fac Trtmnt	*Range: 10k to 100k*		
4X	*Add'l sites*		*$ 142,000*

Additional Annual Costs

Item	Count	Unit Cost	Total
Smpl Rnd	4	$ 1,000	$ 4,000
Rpting	1	$ 2,400	$ 2,400
O&M	3	$ 900	$ 2,700
		Total	*$ 9,100*
4X	*Add'l sites*		*$ 36,400*

Large GWDP Sites
POTW sites, usually publicly owned

Additional Capital Costs

Item	Count	Unit Cost	Total
Mon Well	4	$ 12,000	$ 48,000
Priv Well Svy	1	$ 5,000	$ 5,000
POE-PFAS	6	$ 3,000	$ 18,000
		Total	*$ 71,000*
Fac Trtmnt	*Flows too large*		
2X	*Add'l sites*		*$ 142,000*

Additional Annual Costs

Item	Count	Unit Cost	Total
Smpl Rnd	8	$ 1,000	$ 8,000
Rpting	1	$ 2,400	$ 2,400
O&M	6	$ 900	$ 5,400
		Total	*$ 15,800*
2X	*Add'l sites*		*$ 31,600*

Multiplier 2.3

Additional Capital Costs

Add'l at new PFAS stds	$	4,100,900

Additional Annual Costs

Add'l at new PFAS stds	$	849,160

5x sites

Fac Trtmnt Range : up to $2,100,000	

*Small Facilities only

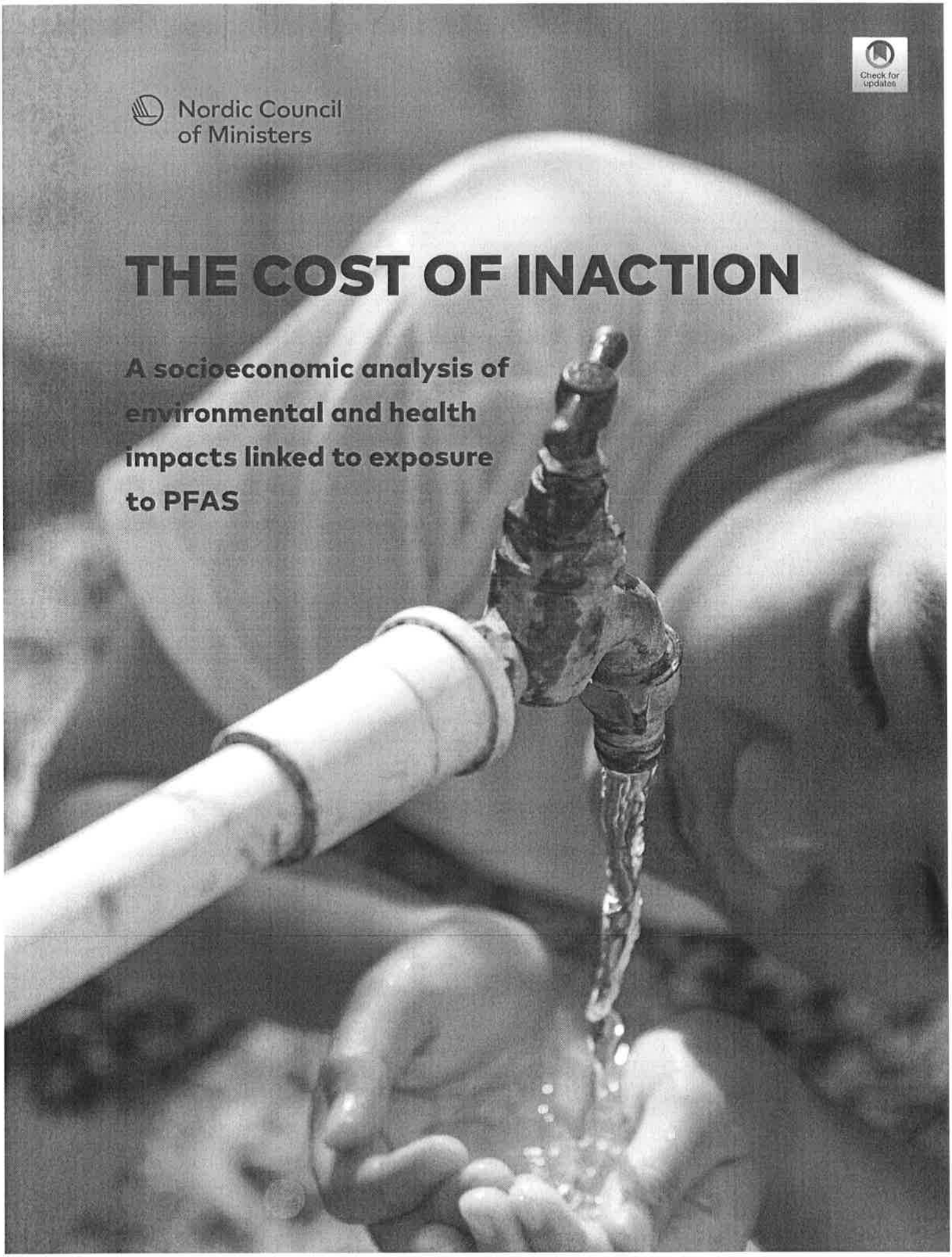
New PFAS Standard Evaluated:
PFOA: 12 ppt
PFOS: 15 ppt
PFNA: 11 ppt
PFHxS: 19 ppt

SUMMARY

For change to lower PFAS standards:
- A total of 27 GWDP sites with PFAS compliance issues - projected across full list of GWDP sites is 37.
-Adds ~ $4.1M to capital costs
-Adds ~ $900K to annual costs

Sites with Existing PFAS issues:
-Potential additional costs to sites with existing compliance issues that exceed the current PFAS standard : ~$800K

Cost impact to small (mostly privately owned) GWDP sites could be greater if WW pre-treatment is put in place: estimate ~ $2M to capital costs


Nordic Council
of Ministers
Check for updates
THE COST OF INACTION
A socioeconomic analysis of environmental and health impacts linked to exposure to PFAS

Summary

This study investigates the socioeconomic costs that may result from impacts on human health and the environment from the use of PFAS (per and polyfluoroalkyl substances). Better awareness of the costs and long-term problems associated with PFAS exposure will assist authorities, policy-makers and the general public to consider more effective and efficient risk management.

The production of PFAS, manufacture and use of PFAS-containing products, and end-of-life disposal of PFAS have resulted in widespread environmental contamination and human exposure. PFAS have been found in the environment all around the world and almost everyone living in a developed country has one or more PFAS in his/her body.

Because of the extreme persistence of PFAS in the environment, this contamination will remain on the planet for hundreds if not thousands of years. Human and environmental exposure will continue, and efforts to mitigate this exposure will lead to significant socioeconomic costs – costs largely shouldered by public authorities and ultimately taxpayers.

The focus of this study is on the costs of inaction with respect to regulation of PFAS in the countries comprising the European Economic Area (EEA). Costs of inaction are defined as the costs that society will have to pay in the future if action is not taken to limit emissions of PFAS today. The PFAS covered in this study are the C4-14 non-polymer fluorosurfactants.

The goal for the study has been two-fold:

1. to establish a framework for estimating costs for society related to negative impacts on health and the environment associated with PFAS exposure; and
2. to provide monetary values for those societal costs, documented by case studies.

Conclusions

The work of estimating the health and environment-related costs to society related to PFAS exposure has relied on the development of assumption-based scenarios. This reflects the limited data available in the academic literature, government documents and press reports. Whilst the uncertainties of the analysis need to be acknowledged, it is also important to recognise that, for several issues, there is little or no uncertainty:

1. PFAS are ubiquitous in the environment, and almost all people have PFAS in their bodies today. Monitoring in both Sweden and the USA concludes that around 3% of the population are currently exposed above proposed limit values, primarily through contamination of drinking water but also via other sources;
2. Many sources of PFAS exposure exist, linked to specialist applications (e.g. AFFFs for firefighting at airports and some industrial locations) and non-specialist uses (e.g. use in consumer goods such as pizza boxes, clothing and cosmetics);
3. Non-fluorinated alternatives for many of these uses are already on the market, and therefore certain uses of PFAS can be reduced;
4. The costs for remediating some cases of contamination run to many millions of EUR. Total costs at the European level are expected to be in the hundreds of millions of EUR as a minimum;
5. A large and growing number of health effects have been linked to PFAS exposure and evidence is mounting that effects occur even at background level exposures.

Current and proposed limit values for drinking water may be further reduced in recognition of growing information on, health and environmental risks. This would increase the costs of environmental remediation estimated here.

As explained throughout the study, the calculations rest on a number of assumptions, though these have been checked against e.g. data on costs incurred to ensure that they are linked to real-world experience. As more information becomes available, calculations will become more precise. Moreover, these findings are conservative. The figures are likely to get larger, in that the numbers of PFAS on the market and the volumes produced keep increasing. Further inaction will lead to more sources of contamination, more people exposed, and higher costs for remediation. The longer that PFAS contamination remains in the environment without remediation, the wider it will spread and the greater the quantity of soil or groundwater that will need to be decontaminated.

Methodology

Two methodologies have been developed, one for estimating health-related costs, the other for estimating costs of environmental remediation. Both methodologies are based on cases concerning exposure to PFAS. Data from the Nordic countries have been used when available, but the estimates also draw on cost data from other European countries, the USA and Australia, where relevant.

Impact pathways (the case studies)

Five case studies following the life-cycle of PFAS, from their production and use in product manufacturing, to the product's use and end-of-life disposal are used to illustrate how exposures to humans and the environment occur. Other instances of PFAS contamination provide additional data on direct costs incurred.

Case Study 1 considers exposures due to the production of PFAS in Europe. It reviews pollution linked to the Chemour factories in Dordrecht, Netherlands, the Miteni facility in the Veneto region of Italy, and the 3M plant near Antwerp, Belgium. The study estimates that up to 20 facilities actively produce fluorochemicals in Europe, that these facilities are significant sources of PFAS released to the environment, and that the exposure of workers at these plants is high.

The impacts from the manufacture and commercial use of PFAS-containing products are the focus of Case Study 2. Industrial activities with the potential to release PFAS to the environment include textile and leather manufacturing; metal plating, including chromium plating; paper and paper product manufacturing; paints and varnishes; cleaning products; plastics, resins and rubbers; and car wash establishments. The study assumes that a range of 3% to 10% of these facilities use PFAS. The study did not identify any fluorochemical production facilities in the Nordic countries. However, Eurostat statistics indicate that other industrial activities with the potential to release PFAS to the environment do take place in the region, such as metal plating and manufacture of paper products.

Case Studies 3 and 4 consider the use phase of PFAS-containing products. Case Study 3 examines exposure to PFAS-containing aqueous film-forming foams (AFFFs) used in firefighting drills and to extinguish petroleum-based fires. The AFFFs have contributed to groundwater contamination, especially around airports and military bases. Nearby communities have been affected by elevated levels of PFAS in their drinking water. Case Study 4 looks at PFAS-treated carpets, PFAS-treated food contact materials, and cosmetics as examples of how a product's use is likely to lead to direct human exposure through ingestion and dermal absorption. The use of products also result in releases to the environment when the product is washed off or laundered, entering sewers and treatment plants, and eventually waterways.

Case Study 5 looks at end-of-life impacts of PFAS-treated products. Municipal waste incineration may destroy PFAS in products if 1000 °C operating temperatures are reached. If landfilled, the PFAS will remain even after the product's core materials break down. The compounds will eventually migrate into liquids in the landfill, then into leachate collection systems or directly into the natural environment. They may then contaminate drinking water supplies, be taken up by edible plants and bioaccumulate in the food chain.

Health-related costs to society

To calculate health-related costs to society, the researchers looked for consensus regarding health endpoints affected by exposure to PFAS. Reviews of the scientific evidence have reached contradictory conclusions about the relevant health endpoints of human exposure to PFAS. However, some consensus has emerged concerning liver damage, increased serum cholesterol levels (related to hypertension), decreased immune response (higher risk of infection), increased risk of thyroid disease, decreased fertility, pregnancy-induced hypertension, pre-eclampsia, lower birth weight, and testicular and kidney cancer.

The methodology draws upon risk relationships developed in the course of specific epidemiological studies for populations exposed to PFAS at different levels. Workers exposed to PFAS in the workplace were used to exemplify a high level of exposure. Communities affected by PFAS, e.g. because of proximity to manufacturing sites or sites where fluorinated AFFFs were used, were assumed to have been exposed at a medium level; this level of exposure was assumed to have been experienced by 3% of the European population. The general population was considered to have experienced exposure at low (background) levels.

Table 1 provides an overview of the estimated annual costs for just a few health endpoints where risk ratios were available for affected populations. For example, the annual health-related costs for the elevated risk of kidney cancer due to occupational exposure to PFAS was estimated to be on the order of EUR 12.7 to EUR 41.4 million in the EEA countries. The estimated costs were substantially higher for elevated and background levels of exposure due to the greater number of persons affected. The total annual health-related costs, for the three different levels of exposure, was found to be at least EUR 2.8 to EUR 4.6 billion in the Nordic countries and EUR 52 to EUR 84 billion in the EEA countries.[1] Despite the high level of uncertainty and the assumptions underlying the calculations, the findings suggest that the health-related costs of exposure to PFAS are substantial.

[1] The health-related costs due to occupational exposure to PFAS in the Nordic countries was not estimated due to an absence of information about the number and location of chemical production plants or manufacturing sites.

Table 1: Estimates of annual health impact-related costs (of exposure to PFAS)

Exposure level	"Exposed" population and source	Health endpoint	Nordic countries		All EEA countries	
			Population at risk	Annual costs	Population at risk	Annual costs
Occupational (high)	Workers at chemical production plants or manufacturing sites	Kidney cancer	n.a.	n.a.	84,000–273,000	EUR 12.7–41.4 million
Elevated (medium)	Communities near chemical plants, etc. with PFAS in drinking water	All-cause mortality	621,000	EUR 2.1– 2.4 billion	12.5 million	EUR 41–49 billion
		Low birth weight	8,843 births	136 births of low weight	156,344 births	3,354 births of low weight
		Infection	45,000 children	84,000 additional days of fever	785,000 children	1,500,000 additional days of fever
Background (low)	Adults in general population (exposed via consumer products, background levels)	Hypertension	10.3 million	EUR 0.7– 2.2 billion	207.8 million	EUR 10.7–35 billion
Totals			*Nordic countries*	*EUR 2.8–4.6 billion*	*All EEA countries*	*EUR 52–84 billion*

Some overlap occurs in the figures above, because workers and affected communities are also exposed to background levels of PFAS. At the same time, these costs are likely to be underestimates due to the lack of epidemiological-based risk relationships for calculating other health endpoints and related costs.

Non-health (environment-related) costs to society

The second methodology compiled information on direct costs incurred by communities taking measures to reduce PFAS exposure through remediation of drinking water. Based on these direct costs, ranges of costs per persons affected or per case were developed. These unit costs then became the foundation for aggregating the costs of remediation when environmental contamination, e.g., PFAS concentrations in drinking water, reach certain levels. It should be noted that the ranges are broad, even when normalized against population.

The approach to derive ranges for the mean is dependent on the amount of data available. For the costs of water treatment, for example, several estimates were available, and in such cases it is unlikely that the true mean will be at either extreme of the range from the studies. Therefore, it is reasonable to truncate the observed range, for example by removing estimates that are sufficiently removed from other data as to be considered outliers. For some costs, however, very few estimates are available, each of which may be equally valid for representation of the average: in such a case the observed range in values is adopted as the range of plausible mean values.

Where no range is available from the studied literature, a range has been estimated. For example, the range of +/-90% is used for establishing a health assessment regime (here considered as a non-health cost as it deals with management of the problem, rather

than impacts on the health of society). In this example, the range is extremely broad for two reasons, first because of the lack of data available and second because of the potential for variation in the implementation of a health assessment programme.

As with the health-based estimates, the study assumes that 3% of the European population is exposed to drinking water with PFAS concentrations over regulatory action levels, such that the water treatment works serving them will require upgrading and maintenance over the next 20 years. The assumption of 20 years reflects potential for remediation to resolve problems perhaps through decontamination or the use of alternative supplies, or the potential for remedial action to persist for many years. Recognising the uncertainties that exist in the analysis and the available data, costs of remediation have been quantified using a scenario-based approach. For each scenario a number of parameters are specified, relating for example to the size of the affected population and the duration of maintenance works.

Table 2 shows the range of costs for the various categories of actions related to environmental remediation.

Table 2: Summary of estimates of mean cost data for non-health expenditures, 20 years

Action taken when PFAS found	Unit	Best estimate	Range from studies	Adopted range
Monitoring – checks for contamination due to industrial or AFFF use	Cost per water sample tested	EUR 340	EUR 278–402	EUR 278–402
	Cost/case of contamination	EUR 50,000	EUR 5,200–5.8 million	EUR 25,000–500,000
Health assessment (including biomonitoring)	Cost/person	EUR 50	No range	EUR 5–95 (+/-90%)
	Total biomonitoring and health assessment per case where considered appropriate	EUR 3.4 million	EUR 2.5 million–4.3 million	EUR 1 million–5 million
Provision of temporary uncontaminated supply	Cost/person	No relevant data		
Provision of a new pipeline	Cost/person	EUR 800	EUR 37–5,000	EUR 100–1,500
Upgrading water treatment works (capital)	Cost/person	EUR 300	EUR 8–2,200	EUR 18–600
Upgrading water treatment works (maintenance)	Cost/person	EUR 19	EUR 8–30	EUR 8–30
Excavation and treatment of soils – contamination from industrial or AFFF use	Cost/kg PFAS	EUR 280,000	EUR 100,000–4.3 million	EUR 100,000–1 million
	Cost/case	EUR 5 million	EUR 100,000–3 billion	EUR 300,000–50 million

In Table 3 the range of costs for the various categories of actions related to environmental remediation for the five Nordic countries are shown. The overall range of costs is EUR 46 million – 11 billion.

Table 3: Detailed breakdown of ranges for non-health costs to the Nordic countries, assuming that 1 to 5% (best estimate 3%) of the population is exposed above a statutory limit and that water treatment is required over a 20 year period

	N people affected (3%)	Screening and monitoring	Health assessment	Upgrade treatment works and maintenance	Soil remediation	Total
Denmark	170,000	EUR 70,000–8.3 million	EUR 280,000–27 million	EUR 7.4 million–274 million	EUR 0–798 million	EUR 8 million–1.1 billion
Finland	160,000	EUR 250,000–22 million	EUR 270,000–26 million	EUR 7.2 million–265 million	EUR 2.2 million–2.1 billion	EUR 10 million–2.4 billion
Iceland	10,000	EUR 10,000–900,000	EUR 20,000–1.6 million	EUR 400,000–1.6 million	EUR 100,000–86 million	EUR 1 million–105 million
Norway	160,000	EUR 170,000–20 million	EUR 260,000–25 million	EUR 6.8 million–250 million	EUR 1.6 million–1.9 billion	EUR 9 million–2.2 billion
Sweden	290,000	EUR 480,000–47 million	EUR 490,000–46 million	EUR 13 million–472 million	EUR 4.3 million–4.5 billion	EUR 18 million–5.1 billion
Nordic total	*790,000*					*EUR 46 million–11 billion*

The cost estimates provided in the table are likely to be more robust at the aggregate, European level than at the national level.

Table 4 provides aggregated costs covering environmental screening, monitoring (where contamination is found), water treatment, soil remediation and health assessment for the five Nordic countries and for the other EEA countries and Switzerland.

Table 4: Aggregated costs covering environmental screening, monitoring where contamination is found, water treatment, soil remediation and health assessment

	Best estimate	Low	High
Denmark	EUR 145 million	EUR 8 million	EUR 1.1 billion
Finland	EUR 214 million	EUR 10 million	EUR 2.4 billion
Iceland	EUR 12 million	EUR 1 million	EUR 105 million
Norway	EUR 194 million	EUR 9 million	EUR 2.2 billion
Sweden	EUR 423 million	EUR 18 million	EUR 5.1 billion
Other EEA+CH	EUR 15,9 billion	EUR 776 million	EUR 159.9 billion
Total	EUR 16.9 billion	EUR 821 million	EUR 170.8 billion

Parallel calculations for all 31 EEA Member Countries and Switzerland arrive at a range of costs for environmental remediation totalling EUR 821 million to EUR 170 billion. The

lower and upper bounds should be considered illustrative because of the limited information available. However, based on the literature review, there is a firm basis for concluding that the lower bound estimates would be exceeded. A best estimate in the order of EUR 10–20 billion is certainly plausible. The potential for higher costs is also possible: An estimate of the costs for one case identified in the course of the research, concerning the town of Rastatt in Baden-Wurttemberg in Germany is in the range of EUR 1 to 3 billion, with the estimated extent of the problem being seen to increase over time. The source of contamination in this case is understood to be contaminated waste paper materials that were spread on agricultural land, demonstrating that serious problems are not always linked to airfields and PFAS manufacture.

A number of other costs related to PFAS contamination are outside the scope of the quantification carried out in this report. These include loss of property value, reputational damage to a polluting company, ecological damage and the costs incurred by public authorities in responding to affected communities – including public outreach, surveys of contamination and remedial measures.

ATTACHMENT 3

Letter from NH Department of Justice dated 6/26/2019 Regarding NHDES Interpretation of RSA 485:3, I(b)

June 28, 2019

ATTORNEY GENERAL
DEPARTMENT OF JUSTICE

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CONCORD, NEW HAMPSHIRE 03301-6397

GORDON J. MACDONALD
ATTORNEY GENERAL

JANE E. YOUNG
DEPUTY ATTORNEY GENERAL

June 26, 2019

Clark Freise
Assistant Commissioner
New Hampshire Department of Environmental Services
29 Hazen Drive
P.O. Box 95
Concord, New Hampshire 03302-0095

Re: NHDES Interpretation of RSA 485:3, I(b)

Dear Assistant Commissioner Freise

In response to the Department of Environmental Service's request for a legal opinion regarding the Department's interpretation of the costs and benefits clause included in RSA 485:3, I(b), as amended by Laws 2018, ch. 368, the Office of Attorney General provided a privileged and confidential letter containing legal advice to the Department. Without waiving the attorney-client privilege, this letter serves as confirmation that the Office of the Attorney General finds the Department's interpretation of RSA 485:3, I(b) to be reasonable and lawful.

Sincerely,

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Environmental Protection Bureau
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CGA/cga